Surfing the waves of Parkinson's disease

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Surfing the waves of Parkinson's disease

Understanding and treating anxiety in the context of motor symptoms

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Surfing the waves of Parkinson's disease
Understanding and treating anxiety in the context of motor symptoms

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Voor opa

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General Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with a prevalence of 100 to 200 per 100,000 people and an annual incidence of 15 per 100,000 people [1]. Due to ageing and accompanying factors such as genetic mutations and environmental risk factors (e.g. pesticides), the occurrence of PD is increasing [1, 2]. Recently, PD has even been described as a pandemic [3].

PD was first described by James Parkinson in 1817 [4] as a neurological syndrome characterized by involuntary tremors and muscular weakness. He also stated '*the senses and intellects being uninjured*' [4]. However, Jean-Martin Charcot described PD as not only showing tremors, but also bradykinesia, autonomic dysfunction, and pain [5]. Furthermore, together with one of his students in 1892, he described depression and hallucinations in PD patients with dementia, as reported by Walusinski [6]. Nowadays, PD is characterized by its main motor symptoms bradykinesia, rigidity and tremor, and additional motor and non-motor symptoms. Non-motor characteristics may include cognitive dysfunction, autonomic failure, and neuropsychiatric symptoms and disorders such as anxiety, depression, psychosis, impulse control disorders, sleep disorders, and apathy [7, 8].

According to Braak and colleagues [9], PD is caused by a neuropathological process, affecting serotonergic, noradrenergic, cholinergic, and dopaminergic systems. This neuropathological process is defined by the accumulation of the protein alpha-synuclein into so-called Lewy bodies, that spread out through the brain in a caudal (brainstem) to rostral (neocortex) gradient [9, 10]. This neurodegenerative process also affects the neurotransmitter systems. When over 60% of dopaminergic neurons of the basal ganglia have degenerated, the motor symptoms on which the clinical diagnosis of PD is based, appear [11]. Together with the affected dopaminergic system, the affected serotonergic, noradrenergic, and cholinergic systems are postulated to cause other motor and autonomic and neuropsychiatric symptoms.

As compared to the motor symptoms, neuropsychiatric symptoms are often reported to have a higher impact on quality of life of both patients and their caregivers [12-15]. Amongst neuropsychiatric symptoms, anxiety and depression are considered major predictors of quality of life, followed by cognitive dysfunction [13, 14]. The lifetime prevalence of an anxiety disorder in PD patients is 49% [16], depression occurs in up to 50% of PD patients at some point in the course of the disease [8], and up to 80% of PD patients develop PD dementia [17, 18].

Debilitating neuropsychiatric symptoms are common, also without fulfillment of the criteria for specific disorders. Clinically relevant anxiety and depressive symptoms occur in 11-26% [19, 20] and 35% of patients [21], respectively.

The neurodegenerative process whereby neurotransmitter systems are extensively affected, and the high prevalence and impact of neuropsychiatric symptoms indicate that non-motor symptoms are an important part of the disease, in addition to the motor symptoms on which the PD diagnosis is mainly based.

Anxiety in PD

Currently, up to 45% of PD patients experience either clinically relevant anxiety symptoms or fulfill the criteria for an anxiety disorder, including generalized anxiety disorder, panic attacks, and social phobia [20, 22, 23].

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [24], anxiety disorders are characterized by certain affective, cognitive, physical, and behavioral symptoms. Affective symptoms include feeling nervous, fear of losing control, and feeling scared. Cognitive symptoms include ruminating, negative bias, and poor concentration. Physical symptoms include muscle tension, sweating, trembling, shortness of breath, and heart palpitations, amongst many others. Lastly, behavioral symptoms include avoidance and safety behaviors.

Diagnosing anxiety in PD is complicated. Physical symptoms of anxiety can be interpreted as motor or autonomic symptoms as part of the disease itself (e.g., tremor, rigidity, freezing, excessive daytime sweating) [25, 26]. In addition, anxiety frequently occurs comorbid or secondary to depression, psychosis, and cognitive decline [23, 27-29].

Detecting and quantifying anxiety can be done with self-report questionnaires, such as the Beck Anxiety Inventory (BAI) [30]. However, due to overlapping anxiety and PD-specific symptoms, and comorbidity with other neuropsychiatric symptoms, the interpretation of the total score on such self-report questionnaires in PD is complicated [25, 26] and raises the question whether these measures are suitable for investigating anxiety in PD [31]. Since it appears to be a complicated construct in PD, anxiety can be both over- as well as underdiagnosed in clinical practice [32, 33].

The interplay between anxiety and motor symptoms

Anxiety in PD can also occur in the context of fluctuations in PD symptoms and is often dependent on available dopamine related to the timing of PD medication. First line treatment for PD symptoms is dopamine replacement therapy (DRT), e.g., levodopa [34]. In reaction to chronic DRT and due to the progressive nature of PD, patients eventually develop response fluctuations, including wearing-off. Wearing-off refers to the re-emergence of PD symptoms while transitioning from an 'on' state to an 'off' state, and typically occurs prior to the next scheduled dose of dopaminergic medication taking effect [35]. About 75% of patients with motor fluctuations experience fluctuations in mood and/or anxiety in parallel [36, 37]. Wearing-off related anxiety is characterized not only by subjective feelings of anxiety but also by physical complaints, such as sweating, abdominal distress and shortness of breath, and can include panic attacks [16]. Just like wearing-off related anxiety, fear of falling is a PD specific anxiety phenomenon associated with motor fluctuations [19, 35, 38].

Anxiety itself can worsen motor symptoms, such as tremor and freezing [39, 40] and a vicious cycle can emerge, in which motor symptoms trigger anxiety or distress, which can in turn exacerbate motor symptoms. As one can imagine, this interplay between motor and anxiety symptoms considerably complicates diagnosing and treating anxiety in PD.

Treatment of anxiety in PD

Evidence for the treatment of anxiety in PD patients is extremely limited [41-43]. No randomized controlled trials (RCTs) with anxiety as primary outcome measure have been performed. Only two studies, without control conditions, have been performed to investigate the effect of psychotherapy on anxiety in PD [44, 45]. Psychotherapy includes cognitive behavioral therapy (CBT) and mindfulness based treatments. Their effects on psychological distress (including anxiety) are reviewed and analyzed in **chapter 6** [46].

Similar to psychotherapy, pharmacological treatments of anxiety in PD have not been investigated using RCT research designs. Non-RCT studies using serotonergic antidepressants have reported marginal secondary benefits for anxiety symptoms in PD, and treatment with benzodiazepines should be used with caution because of their propensity to increase cognitive impairment and risk of falling [8]. For patients who experience anxiety as part of an 'off' state, or as non-motor fluctuation, dopaminergic medication adjustments can be made in an attempt to decrease the duration and severity of these 'off' episodes [8, 43, 47]. However, the risk of

developing a dopamine dysregulation syndrome (DDS) is worth noticing, which refers to compulsive PD medication overuse. DDS is associated with wearing-off related anxiety and can develop after continually taking extra PD medication (which can be described as avoidance behavior) to prevent the debilitating 'off' state [48].

Since anxiety in PD is complex due to its reciprocal interactions with motor symptoms, treatment should preferably be multidisciplinary and integrated. Current treatment options seem inadequate and there is a need for further investigation and development [8, 13, 14, 49]. Not only the treatment of anxiety symptoms, but also the diagnosis, phenomenology, origin, contributing factors, and underlying mechanisms of anxiety in PD are in high need of further research.

Aims & outline thesis

The overall aim of this thesis was to investigate the phenomenology, associations and interactions, and treatment of anxiety in relation to motor and other non-motor symptoms in PD patients.

Part 1 (chapters 2 through 5) focuses on understanding the complex associations and interactions between anxiety, motor and other non-motor symptoms in PD. This can contribute to an improvement of the diagnosis of anxiety and help developing adequate treatment options for PD related anxiety. Subsequently, part 2 (chapters 6 through 8) focuses on the role of psychotherapy for reducing symptoms of psychological distress (including anxiety) in PD patients, and investigates a newly developed multidisciplinary treatment to address interacting motor and anxiety symptoms.

Part 1

In **chapter 2** we investigate the phenomenology of anxiety in PD by performing a principal component analysis to explore underlying symptom dimensions of anxiety as measured with the BAI [50]. These symptom dimensions can be considered subscales of anxiety. We also describe the associations of the resulting subscales with motor, autonomic, and depressive symptoms. Insight in the phenomenology of anxiety in PD patients, and its relatedness to other motor and non-motor symptoms, can improve recognition and diagnosis of anxiety in clinical practice.

To investigate the generalizability of the findings in chapter 2, **chapter 3** describes the replication of the principal component analysis in a PD patient population referred for neuropsychiatric evaluation to a specialized psychiatric outpatient department [Ghielen et al., 2020 (under review)]. In order to investigate the clinical

implication of the replicated findings, we additionally performed a post-hoc analysis in which we investigated the predictive value of the principal component with the highest percentage of explained variance in whether or not patients received an anxiety disorder diagnosis.

Chapter 4 compares two symptom networks of anxious versus non-anxious PD patients, including anxiety and motor symptoms. We investigated whether anxiety and motor symptoms are more strongly connected in the anxious PD patient sample, compared to the non-anxious PD patient sample [Ghielen et al., 2020 (submitted)]. To test this hypothesis, we performed a network comparison test.

The previous chapters demonstrate relationships between anxiety and motor symptoms. However, no conclusions can be drawn concerning their relationships over time. Therefore, in **chapter 5**, we investigate the longitudinal associations between anxiety, fear of falling, and freezing of gait in PD [Ghielen et al., 2020]. In addition, we investigated which confounding factors influenced these associations, to gain further understanding of these relationships.

Part 2
To explore the current state of psychological treatment options, we describe two meta-analyses in which we investigated the effects of cognitive behavioral and mindfulness-based therapies on psychological distress in patients with neurodegenerative disorders in **chapter 6** [46].

Since evidence for the treatment of anxiety in PD patients is extremely limited, and motor and non-motor symptoms appear to interact, especially in PD patients that experience symptom fluctuations, effective psychological treatment, especially multidisciplinary treatment is warranted [8, 13, 14]. Therefore, we developed a new intervention that combines acceptance and commitment therapy with physical therapy, to treat both non-motor and motor symptoms, including their interactions. In this treatment, we included PD patients that experience wearing-off related anxiety. **Chapters 7 & 8** describe the study protocol and subsequent results of a pilot randomized controlled trial in which we describe and investigate the effectiveness and feasibility of this new body awareness treatment (named *BEWARE*) [51, 52].

Finally, in **chapter 9**, a summary is provided of the main findings of this thesis, followed by a general discussion and directions for future research.

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2

Anxiety in Parkinson's disease: symptom dimensions and overlap with depression and autonomic failure

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Abstract

Introduction: Anxiety disorders are highly prevalent in patients with Parkinson's disease (PD) and have a major impact on wellbeing. They nevertheless receive limited scientific attention. This study aimed to establish the symptom dimensions of anxiety in PD, and their relationship with depression, autonomic failure and motor symptoms.

Methods: In this cross-sectional observational study, symptoms of anxiety were measured with the Beck Anxiety Inventory (BAI) in 294 PD patients. Symptom dimensions of anxiety in PD were explored through principal component analysis (PCA) of BAI items. The relationship between anxiety and depressive, autonomic and motor symptoms was assessed through PCA and regression analyses.

Results: Clinically relevant symptoms of anxiety were present in 45% of patients. PCA of the BAI resulted in five subscales, corresponding to a single affective and four somatic symptom dimensions (thermoregulation, hypotension, hyperventilation and trembling) of anxiety. Symptoms of anxiety and depression displayed a large overlap. All somatic BAI subscales were significantly influenced by motor and autonomic symptoms, while the affective subscale was not.

Conclusion: Anxiety in PD comprises affective and somatic symptom dimensions. The affective subscale of the BAI is not influenced by motor or autonomic symptoms, and may therefore prove useful for future research. Scores on the somatic subscales of the BAI were associated with autonomic failure and motor impairment, demonstrating a strong interplay between motor and non-motor symptoms in PD. These results stress the importance of a holistic approach of anxiety in PD.

Introduction

Despite a high prevalence and a major impact on daily functioning and quality of life in patients with Parkinson's disease (PD), anxiety has only recently attracted scientific attention. Estimates suggest that 40-50% of PD patients experience clinically relevant symptoms of anxiety [1, 2], and approximately one third suffers from an anxiety disorder as specified by the Diagnostic and Statistic Manual of mental disorders (DSM) IV-TR criteria [1-4]. Generalized anxiety disorder, social phobia and anxiety disorder not otherwise specified (NOS) are most frequently diagnosed in this population [2, 3, 5]. Anxiety disorders are more common in PD patients than in the general population, in primary care clinics or in patients with other chronic medical conditions, where prevalence rates vary between 5 and 11% [4]. Anxiety in PD patients is associated with increased subjective motor symptoms [6], more severe gait problems [7], dyskinesias [7], freezing [8], motor response fluctuations [6], and a decrease in health-related quality of life [9].

In clinical practice, anxiety disorders are often underdiagnosed in PD patients [10]. In a large proportion of patients with PD that report clinically relevant anxiety, the symptoms do not meet the criteria of a discrete DSM-IV disorder and are therefore classified as an anxiety disorder NOS [3]. This suggests that anxiety disorders may have an atypical presentation in this population. The poor recognition of anxiety might also be explained by the overlap and interaction with PD-related motor and non-motor symptoms, such as depression, motor symptoms and autonomic failure.

An improvement of the diagnostics of anxiety in PD could be aided by an in-depth study of the symptom dimensions covered by self-report questionnaires such as the Beck Anxiety Inventory (BAI) [11] and their relatedness to other motor and non-motor symptoms. Factor analysis is a statistical technique that can help to explore the underlying factors or symptom dimensions covered by a questionnaire. In non-PD samples factor analysis has shown that the BAI comprises cognitive and somatic factors and that the BAI is able to differentiate between symptoms of anxiety and depression [12, 13]. Dimensionality of the BAI in PD patients was only addressed in a single study [14], but no satisfactory factor solution was found, possibly due to the heterogeneity of the study sample.

In the present study, we analyzed the symptom dimensions of the BAI within a large sample of PD patients. Secondly, we assessed the overlap of symptoms of anxiety with depression, autonomic dysfunction and motor disability in PD.

Methods

Subjects

For this cross-sectional study, we used data collected during routine clinical assessments at the outpatient clinic for movement disorders of the VU University medical center (VUmc) in Amsterdam, the Netherlands, between May 2008 and January 2013. In this period, 383 PD patients were assessed. Patients were clinically diagnosed with idiopathic PD using the United Kingdom PD Society Brain Bank (UKPDSBB) criteria. The clinical diagnosis was supported by both magnetic resonance imaging (MRI) and dopamine transporter single-photon emission computed tomography (DAT-SPECT) scans in 244 patients, by MRI only in 37 patients and by DAT-SPECT scan only in 23 patients. In the remaining 79 patients, no brain imaging was performed. All included patients gave written informed consent to use their clinical data for scientific purposes. Patients with severe cognitive decline, defined as a Mini Mental State Examination (MMSE) score < 24, were excluded.

Measurements

Anxiety

Symptoms of anxiety were measured with the BAI. The BAI is a 21-item self-report instrument asking for symptoms of anxiety over the past week [11]. Patients answer on a four-point Likert scale, ranging from 0 (not at all) to 3 (severely). In patients with PD, clinically relevant anxiety is defined as a BAI-score > 12 [14]. This cut-off score is lower than in the general population, due to a lower construct validity of the BAI in PD patients [14].

Clinical and demographic factors

Age, gender and the use of dopaminergic medication (0 = no, 1 = yes) were registered for use in statistical analyses.

The independent variables of major interest were symptoms of depression, motor dysfunction and autonomic failure. We evaluated symptoms of depression with the Beck Depression Inventory (BDI) [15]. Severity of motor symptoms was assessed using section III and V (Hoehn and Yahr stage) of the Unified Parkinson Disease Rating Scale (UPDRS) [16].

We used the Scales for Outcomes in Parkinson's disease – Autonomic (SCOPA-AUT) [17] to assess autonomic failure. The SCOPA-AUT includes five questions on sexual function: item 22, 23 and 23a apply to men, and item 24 and 25 to women. The answers to these questions were unreliable on multiple occasions, e.g. patients

choosing "not applicable" for all five items, or male patients answering question 24 or 25. Therefore, we decided to exclude the sexual items of the SCOPA-AUT from the analyses.

Statistical analyses

We performed all analyses using IBM SPSS Statistics 20 for Windows. The significance level was set at $p < 0.05$ with two-sided testing. Acceptability of missing values on the BAI, BDI and SCOPA-AUT was determined as less than 16.67% of items. In the event of more missing data, we excluded the patient for the analysis by pair-wise exclusion. When less than 16.67% of data was missing, we filled in missing values by mean imputation. We performed no imputation of missing data on the UPDRS-III, since we considered this to be unreliable for this scale.

In the first analysis, we assessed dimensionality of the BAI with a principal component analysis (PCA). To determine the number of extracted factors we combined the Cuttman-Kaiser Eigenvalue greater-than-one rule and the "scree plot" criterion. We used oblimin rotation because we expected the different factors to correlate with each other. The factors obtained in this analysis can be considered as subscales of the BAI or symptom dimensions of anxiety. Scores on the derived subscales of the BAI were used in further analyses.

Second, we studied the relationship between the BAI, BDI, SCOPA-AUT and UPDRS-III, by conducting multiple linear regression analyses. Assumptions for regression analyses (normality and homoscedasticity of residuals) were checked. Multicolinearity was evaluated with a correlation matrix and calculation of the variance inflation factor (VIF).

The total BAI score was the dependent variable in the first set of regression analyses. In the second set, it was the score on the subscale of the BAI, derived with PCA previously. The independent variables of interest were the total score on the BDI, SCOPA-AUT and UPDRS-III. We conducted all analyses first with only the independent variable of interest (unadjusted model). We then adjusted the model stepwise for age and gender (model 1), use of dopaminergic medication (model 2), and the other two independent variables of main interest, i.e. the BDI, SCOPA-AUT and/or UPDRS-III score (model 3). Finally, we examined confounding in all models.

Results

Of the original sample of 382 PD patients, 75 patients met exclusion criteria (MMSE < 24). An additional 13 patients were excluded from the analyses for not meeting our standards of acceptability of missing values on the BAI. This resulted in a total sample size of 294 patients. Due to missing data on the BDI, UPDRS-III and/or SCOPA-AUT, 3 to 18 additional patients were excluded pair-wise during statistical analyses. The majority of patients was male. Mean age was 64.5 years. Patients had a mean UPDRS-III score of 25.8 and a median Hoehn and Yahr stage of 2. Demographic and clinical characteristics of the sample are given in Table 1.

Table 1. Demographic and clinical characteristics of subjects (*n* = 294)

	Mean	SD	Range
% Female	39.5		
Age	64.5	10.3	27-89
Disease duration (yr)	5.1	5.6	0-40
MMSE score	28.0	1.7	24-30
BDI score	11.4	8.0	0-36
SCOPA-AUT score	35	10.0	0-64
UPDRS-III score	25.8	12.3	2-58
Hoehn & Yahr stage	2 (median)		1-5
% Use dopaminergic medication	48.6		

Occurrence and symptom dimensions of anxiety in PD

The mean score on the BAI was 14.2 (SD 9.8, range 0-50). Forty-five percent of patients in our sample had a BAI score of 12 or more, which is considered to be a clinically relevant level of anxiety [14].

The Eigenvalue >1 criterium suggested that five factors should be extracted. This was confirmed by an inspection of the scree plot (see Figure S1 in the supplementary material). Items 3 'wobbliness in legs', 7 'heart pounding/racing' and 18 'indigestion' had a loading of less than 0.4 on all factors and were therefore excluded from the factor solution.

The five obtained factors were interpreted as *anxiety*, *thermoregulation, hypotension, hyperventilation* and *trembling*. The factor solution explained 62.7% of variance. Figure 1 demonstrates the distribution of the BAI items over the five factors, with corresponding factor loadings.

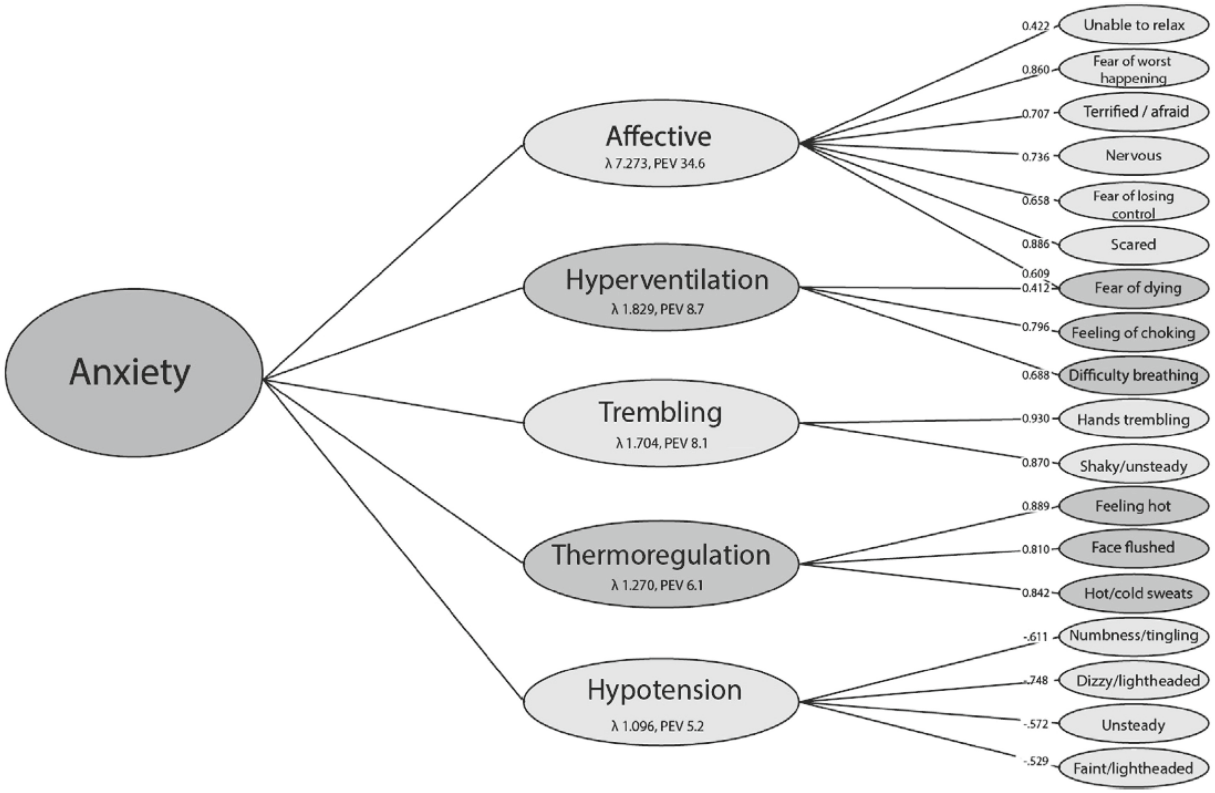

Figure 1. Graphical display of the Exploratory Factor Analysis solution of the BAI. Factor loadings, Eigenvalues (l) and percentage of explained variance (PEV) are displayed.

Associations between anxiety, depression, motor dysfunction and autonomic failure in PD

Histograms demonstrated that the residuals of both the total BAI score and subscales of the BAI had a positively skewed distribution. Transformation of the data did not improve normality. To maintain interpretability of results, we decided to use the original data for the analyses. Homoscedasticity was confirmed by plotting the regression standardized predicted value against the regression standardized residual. Both the correlations (see Table 2) and the VIF (ranging from 1.005 to 1.610) indicated non-collinearity of the data.

Table 2. Matrix of the Pearson's correlation coefficients (r) for the BAI, BDI, SCOPA-AUT, UPDRS-III and age.

	BAI	BDI	SCOPA-AUT	UPDRS-III	Age
BAI	1.000	0.735**	0.616**	0.234**	0.100
BDI	0.735**	1.000	0.535**	0.230**	0.120*
SCOPA-AUT	0.616**	0.535**	1.000	0.330**	0.277**
UPDRS-III	0.234**	0.230**	0.330**	1.000	0.300**
AGE	0.100	0.120*	0.277**	0.300**	1.000

**p-value < 0.05, **p-value < 0.01 (2-tailed).*

Results of the multiple regression analyses with the BAI total score and subscales of the BAI as dependent variable are presented in Table 3. In this table, the final, adjusted models are displayed, showing the influence of each independent variable on the outcome variable. The unadjusted and adjusted models, including detailed information on confounding, can be found in Supplementary Table S1.

The BAI total score was significantly influenced by age and gender: younger patients and females had a higher score on the BAI than older patients and men. The BAI score also increased with a higher score on the BDI and SCOPA-AUT. The UPDRS-III score no longer significantly influenced the BAI score after adjustment for score on the BDI and SCOPA-AUT.

All subscales of the BAI were influenced by the BDI score. Moreover, the subscales *thermoregulation* and *hyperventilation* were significantly influenced by the SCOPA-AUT, the *trembling* subscale by the UPDRS-III, and the *hypotension* subscale by both. The *affect* subscale was only significantly influenced by the BDI score, and not by the SCOPA-AUT and UPDRS-III. The relationship between the BAI total score and the subscales of the BAI and the BDI, SCOPA-AUT and UPDRS-III were influenced by confounders, as mentioned in the addendum of Supplementary Table

Table 3: Results of multiple linear regression analysis of the BAI total score and score on subscales of the BAI with the BDI, SCOPA-AUT and UPDRS-III. Regression coefficients (B) with 95% confidence intervals (95%-CI of B), standardized regression coefficients (β) and significance (indicated with *) are displayed for the final model.

Independent variable →	***BAI total score***			***Subscale Affective***			***Subscale Thermoregulation***		
Dependent variable ↓	**B**	**95%-CI of B**	β	**B**	**95%-CI of B**	β	**B**	**95%-CI of B**	β
(Constant)	-1.053	-6.086 – 3.979		1.968	-.648 - 4.584		1.074	-.360 – 2.508	
BDI	0.688	0.582 – 0.794	0.560***	0.373	0.318 – 0.428	0.678***	0.050	0.020 – 0.080	0.193**
SCOPA-AUT	0.397	0.294 – 0.501	0.352***	0.046	-.008 – 0.100	0.092	0.098	0.069 – 0.128	0.416***
UPDRS-III	0.026	-.037 – 0.089	0.033	-.010	-.043 – 0.022	-.029	-.005	-.023 – 0.013	-.031
Gender	-2.198	-3.666 – -.730	-.110**	-.682	-1.445 – 0.081	-.076	-.488	-.906 – -.070	-.116*
Age	-.082	-.156 – -.007	-.086*	-.028	-.067 – .010	-.067	-.050	-.072 – -.029	-.253
Use of dopaminergic medication	-1.457	-2.959 – .045	-.074	-.890	-1.671 – -.110	-.101*	0.159	-.268 – 0.587	0.039
R^2	0.629			0.499			0.311		

** p-value <0.05, ** p-value < 0.01, *** p-value < 0.001*
R^2 = proportion variance of independent variable explained by the regression model

Table 3 (continued)

Independent variable →	***Subscale Trembling***			***Subscale Hyperventilation***			***Subscale Hypotension***		
Dependent variable ↓	**B**	**95%-CI of B**	β	**B**	**95%-CI of B**	β	**B**	**95%-CI of B**	β
(Constant)	-.828	-2.144 – 0.487		-1.004	-1.680 – -.329		-1.890	-3.373 – -.406	
BDI	0.056	0.029 – 0.084	0.256***	0.022	0.008 – 0.036	0.191**	0.105	0.074 – 0.136	0.335***
SCOPA-AUT	0.024	-.003 – 0.051	0.117	0.040	0.026 – 0.054	0.374***	0127	0.096 – 0.157	0.441***
UPDRS-III	0.027	0.011 – 0.044	0.189***	-.001	-.010 – 0.007	-.016	0.019	0.001 – 0.038	0.094*
Gender	-.163	-.547 – 0.221	-.045	0.076	-.121 – 0.273	0.040	-.476	-.908 – -.043	-.093*
Age	0.019	0.000 – 0.039	0.112	-.004	-.014 – 0.006	-.042	-.009	-.031 – 0.013	-.037
Use of dopaminergic medication	-.547	-.939 – -.154	-.156*	0.076	-.125 – 0.278	0.041	-.157	-.599 – 0.286	-.031
R^2	0.208			0.255			0.502		

** p-value <0.05, ** p-value < 0.01, *** p-value < 0.001*
R^2 = proportion variance of independent variable explained by the regression model

S1. The confounding variables were age and the BDI, SCOPA-AUT and UPDRS-III score. Although, as demonstrated in Table 2, these variables were all significantly correlated with each other, VIF remained within acceptable bounds.

Discussion

In this study, clinically relevant symptoms of anxiety were present in 45% of patients in our sample, which corresponds with previously reported rates [1, 2]. PCA of the BAI revealed one affective and four somatic symptom dimensions (*thermoregulation, hypotension, hyperventilation* and *trembling*) of anxiety. The finding of a distinct affective factor and multiple somatic factors is in line with previous research on dimensionality of the BAI in non-PD samples [11, 13, 18, 19]. In these studies, less than five factors were found, probably because the samples consisted of psychiatric patients with a mean age under 40 years. These patients are less likely to experience somatic symptoms than the patients in our sample, who have a variety of PD-related motor and non-motor symptoms that overlap with somatic anxiety equivalents. Moreover, differences in the methodology of the factor analysis, such as the choice of rotation method, can lead to a different number of obtained factors.

The BDI significantly influenced all subscales of the BAI, as well as the BAI total score. Moreover, there was a high correlation between the BAI and BDI. This suggests that the large overlap between anxiety and depression that is found in psychiatric patients [20], is present in PD patients as well. In previous studies, anxiety and depressive disorders coexisted in 19 to 40% of patients with PD, which is higher than in matched controls [21-23].Autonomic symptoms significantly influenced the total score on the BAI and on the *hypotension, thermoregulation* and *hyperventilation* subscales, while severity of motor symptoms influenced the score on the *trembling* subscale. The most obvious explanation for these observations is that the BAI is designed to measure episodic anxiety, such as in panic disorder, which is accompanied by somatic equivalents of anxiety [19]. Alternatively, symptoms of PD-related autonomic and motor dysfunction might be misinterpreted as anxiety, resulting in overdiagnosis of anxiety disorders in PD patients [24]. In this study, we demonstrated that the score on the *affect* subscale was not influenced by the SCOPA-AUT or the UPDRS-III score. One might therefore conclude that the *affect* subscale constitutes the most reliable measure of anxiety in PD, because it is not affected by 'noise' generated by motor and autonomic symptoms. The use of questionnaires excluding somatic symptoms for the screening of psychiatric disorders in the elderly has been advocated for this reason [25]. In PD patients, however, attempts

to make a clear distinction between autonomic symptoms caused by anxiety and PD-related autonomic dysfunction will probably prove futile. The diagnostic criteria for anxiety disorders underline that physical symptoms comprise an integral part of the syndrome 'anxiety' [26]. Moreover, PD-related autonomic symptoms and anxiety frequently co-occur and overlap in symptomatology [2, 24], and there is an interplay between anxiety and somatic symptoms [2, 3, 24]. The development of autonomic failure in PD may lead to a pathophysiological predisposition towards somatic symptoms of anxiety. This hypothesis is supported by research in non-PD patients suffering from autonomic failure. For example, in patients with pure autonomic failure, hyperventilation causes a larger decrease in blood pressure than in healthy controls [27, 28]. In a case-report on a patient with pure autonomic failure who experienced dizziness during emotional stress, a significant decrease in blood pressure after stressful events was demonstrated [29]. Moreover, PD patients with failure of both the sympathetic and parasympathetic nervous system had higher levels of anxiety and depression than healthy controls or de novo PD patients [30]. One may therefore expect that the presence of autonomic failure in PD patients gives rise to a stronger physical response to anxiety. The presence of anxiety is also associated with an increase in motor symptoms in PD [6-8]. Vice versa, PD-related motor symptoms, such as wearing-off, can give rise to anxiety: a substantial number of PD patients suffers from situational anxiety, with phobic avoidance related to fear of experiencing off-periods or freezing [3]. The clinical finding that many PD patients with response fluctuations experience anxiety and autonomic symptoms during wearing-off [6, 31, 32], suggests that dopaminergic transmission is involved in the etiology of both motor and non-motor symptoms of PD [33, 34]. These findings make the distinction between anxiety and other motor and non-motor symptoms of PD appears artificial. In line with this, the MDS task force on rating scales for PD recommends an "inclusive approach" when rating possible symptoms of anxiety in PD patients, without trying to attribute them to either anxiety or other PD-related symptoms [35]. The finding of an *affect* subscale of the BAI, that is not influenced by motor or autonomic symptoms, might nevertheless be relevant for research purposes. Moreover, our results can be useful in the development of new measures for anxiety in PD.

This study has some limitations. The only measure of anxiety in this study was the BAI. The BAI can be used to assess symptoms of anxiety, but is not a diagnostic instrument. Moreover, the BAI is more suitable for measuring episodic anxiety than the non-episodic anxiety that occurs in generalized anxiety disorder [18], which is one of the most prevalent anxiety disorders in PD patients [2]. Strengths of the present study are the large number of patients included, and the homogeneity of

the sample. Moreover, this is the first study that has successfully performed a factor analysis of the BAI in a sample of PD patients.

Conclusions

In this study, we demonstrated that anxiety in PD patients, as measured with the BAI, comprises one affective and four somatic symptom dimensions. Scores on the BAI and BDI are highly correlated, which can be explained by symptom overlap and frequent co-occurrence of anxiety and depression in PD.

The score on the somatic subscales of the BAI is significantly influenced by autonomic failure and motor dysfunction, whereas the *affect* subscale is not. This finding suggests that the *affect* subscale may be a more reliable measure of anxiety in PD patients. However, somatic symptoms cannot be completely disregarded in the diagnostic process of anxiety disorders. Furthermore, anxiety, autonomic failure and motor dysfunction in PD may share underlying etiological mechanisms. The strong interplay between motor and non-motor symptoms in PD warrants a holistic approach to anxiety in clinical practice. Hopefully, the findings in this study will stimulate the development of new and more specific measures of anxiety in PD.

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Supplementary material Chapter 2

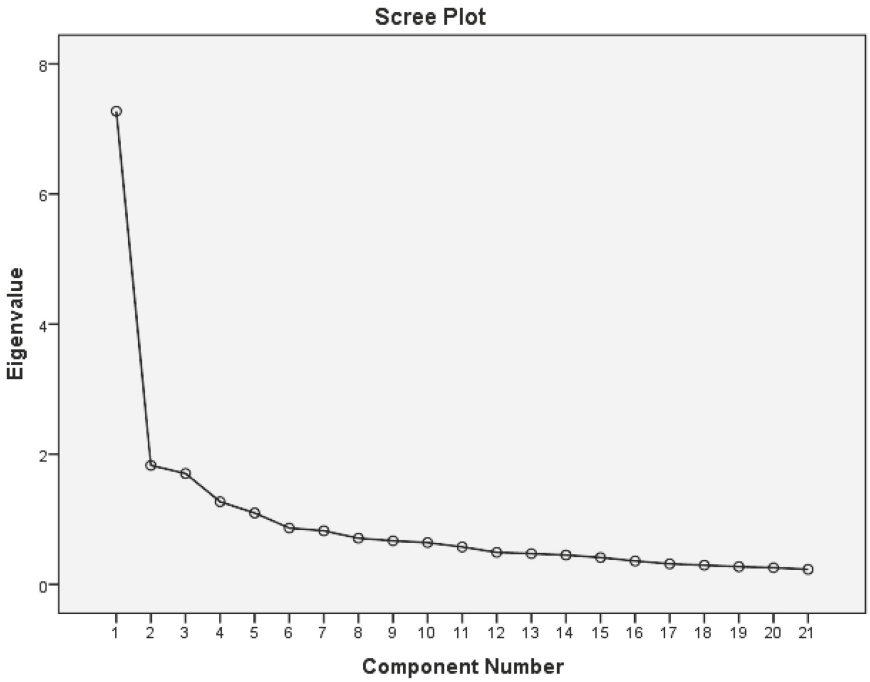

Figure S1: Scree plot of the principal component analysis of the BAI

Table S1: Results of multiple linear regression analysis association BAI total score and score on subscales of the BAI with BDI, SCOPA-AUT and UPDRS-III. All associations are adjusted for covariates in three consecutive models. Regression coefficients (B) and 95% confidence intervals (95%-CI) and significance (p-values, indicated with *) are displayed, as well as information on confounding covariates (Ad 1 – 11).

		Crude model		Model 1		Model 2		Model 3	
		B	**95%-CI**	**B**	**95%-BI**	**B**	**95%-CI**	**B**	**95%-CI**
BAI total score									
BDI	1	0.904***	0.807 - 1.001	0.895***	0.797 - 0.992	0.895***	0.794 - 0.997	0.688***	0.582 - 0.794
SCOPA-AUT	2	0.695***	0.592 - 0.799	0.723***	0.617 - 0.829	0.730***	0.618 - 0.843	0.397***	0.294 - 0.501
UPDRS-III		0.187***	0.096 - 0.277	0.193***	0.099 - 0.288	0.173***	0.079 - 0.268	0.026	-.037 - 0.089
Subscale Affective									
BDI		0.381***	0.335 - 0.428	0.381***	0.335 - 0.428	0.394***	0.346 - 0.442	0.373***	0.318 - 0.428
SCOPA-AUT		0.199***	0.145 - 0.254	0.212***	0.156 - 0.268	0.219***	0.159 - 0.278	0.046	-.008 - 0.100
UPDRS-III		0.042*	0.001 - 0.083	0.047*	0.004 - 0.090	0.042	-.001 - 0.086	-.010	-.043 - 0.022
Subscale Thermoregulation									
BDI	3	0.102***	0.075 - 0.130	0.105***	0.078 - 0.133	0.098***	0.069 - 0.126	0.050**	0.020 - 0.080
SCOPA-AUT	4	0.107***	0.082 - 0.132	0.124***	0.100 - 0.149	0.120***	0.094 - 0.146	0.098***	0.069 - 0.128
UPDRS-III		0.0128	-.007 - 0.032	0.022*	0.002 - 0.042	0.017	-.003 - 0.037	-.005	-.023 - 0.013
Subscale Trembling									
BDI	5	0.075***	0.050 - 0.099	0.069***	0.045 - 0.093	0.076***	0.051 - 0.100	0.056***	0.029 - 0.084
SCOPA-AUT		0.060***	0.038 - 0.083	0.051***	0.028 - 0.074	0.059***	0.035 - 0.084	0.024	-.003 - 0.051
UPDRS-III	6	0.042***	0.026 - 0.058	0.036***	0.020 - 0.053	0.038***	0.021 - 0.055	0.027***	0.011 - 0.044
Subscale Hyperventilation									

Table S1: Continued.

		Crude model		Model 1		Model 2		Model 3	
		B	**95%-CI**	**B**	**95%-BI**	**B**	**95%-CI**	**B**	**95%-CI**
BDI	7	0.045***	0.033 - 0.058	0.045***	0.033 - 0.058	0.042***	0.029 - 0.055	0.022**	0.008 - 0.036
SCOPA-AUT	8	0.050***	0.039 - 0.061	0.052***	0.041 - 0.064	0.050***	0.038 - 0.062	0.040***	0.026 - 0.054
UPDRS-III		0.011*	0.002 - 0.020	0.010*	0.001 - 0.019	0.008	-.001 - 0.017	-.001	-.010 - 0.007
Subscale Hypotension									
BDI	9	0.184***	0.155 - 0.214	0.179***	0.150 - 0.209	0.174***	0.143 - 0.205	0.105***	0.074 - 0.136
SCOPA-AUT	10	0.182***	0.156 - 0.208	0.183***	0.157 - 0.210	0.183***	0.154 - 0.211	0127***	0.096 - 0.157
UPDRS-III	11	0.060***	0.037 - 0.083	0.058***	0.034 - 0.081	0.052***	0.029 - 0.076	0.019*	0.001 - 0.038

** p-value <0.05, ** p-value < 0.01, *** p-value < 0.001*

Model 1: adjustment for age and gender
Model 2: adjustment for age, gender, and use of dopaminergic medication
Model 3: adjustment for age, gender, use of dopaminergic medication, and score on the BDI and/or SCOPA and/or UPDRS-III score

Ad 1: confounding by the SCOPA-AUT score.
Ad 2: confounding by the UPDRS-III score.
Ad 3: confounding by the SCOPA-AUT score.
Ad 4: confounding by BDI score and age.
Ad 5: confounding by SCOPA-AUT score.
Ad 6: confounding by the SCOPA-AUT and BDI score and age.
Ad 7: confounding by the SCOPA-AUT score.
Ad 8: confounding by the BDI score.
Ad 9: confounding by the SCOPA-AUT score.
Ad 10: confounding by the BDI score.
Ad 11: confounding by the SCOPA-AUT en BDI score.

3

Symptom Dimensions of Anxiety in Parkinson's Disease: Replication study in a neuropsychiatric patient population

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Abstract

Introduction: Anxiety disorders occur in approximately one third of people with Parkinson's disease (PD), and have a major impact on patient and caregiver wellbeing. In order to better understand and diagnose anxiety in PD patients, we investigated the generalizability of the results of a previous factor analysis on anxiety symptoms to a sample of PD patients with neuropsychiatric symptoms.

Methods: Anxiety symptoms were measured with the Beck Anxiety Inventory (BAI) in 123 PD patients who were referred for neuropsychiatric diagnostics and treatment. Subscales of anxiety were analyzed through principal component analysis of BAI items. The associations between BAI subscales and motor and other neuropsychiatric symptoms were assessed through regression analyses.

Results: Similar to the previous factor analysis, we found one psychological (affective) and four somatic subscales of anxiety in the BAI. The affective subscale was the principal component explaining 35.9% of the variance. The scores on the total BAI and the affective subscale were significantly associated with depressive symptoms. In a post-hoc analysis, the affective subscale had equal power as compared to the total BAI in predicting whether or not patients received an anxiety disorder diagnosis through psychiatric evaluation.

Conclusion: Anxiety in PD is a complicated construct due to symptom overlap and mutual interactions. The affective subscale of the BAI shows potential as a screening tool for non-episodic anxiety in PD. We highly recommend evaluating anxiety symptoms in the context of other PD symptoms, including motor, autonomic, and other (neuro)psychiatric symptoms.

Introduction

Anxiety disorders are present in an estimated 31% of patients with Parkinson's Disease (PD), with generalized anxiety disorder being the most common [1, 2]. Around 45% of PD patients suffer from clinically relevant anxiety [3]. Both from clinical experience and previous research, anxiety can be linked to fluctuations in available dopamine related to timing of PD medication and is often comorbid or secondary to depression, psychosis, and cognitive decline [3-5]. Anxiety is therefore one of the most prevalent neuropsychiatric features in PD patients and can be very debilitating. In addition, its presence is one of the most significant predictors of health-related quality of life in PD [6, 7], and greatly impacts caregiver burden [8]. Anxiety can worsen motor symptoms, such as tremor and freezing [9, 10] and can create a vicious cycle, in which motor symptoms trigger anxiety or distress, which can in turn exacerbate motor symptoms. These reciprocal interactions between motor and non-motor symptoms are not only seen in clinical practice but are supported by scientific research [11-13]. Despite its large impact on patient well-being and caregiver burden, anxiety in PD is still poorly understood and evidence on the treatment of anxiety in PD patients is limited [14, 15].

Since anxiety and other PD-related symptoms are so highly intertwined, diagnosing anxiety is complicated by its overlap with motor (e.g., tremor, rigidity, freezing) and autonomic symptoms (e.g., excessive daytime sweating) [12, 16]. Self-report questionnaires, such as the Beck Anxiety Inventory (BAI), can be used to quantify anxiety symptoms [17]. Due to the aforementioned reciprocity, the interpretation of the total score on such self-report questionnaires can be complicated. Evaluation of the specific symptom dimensions (or subscales of a questionnaire) can be a useful approach [18]. One statistical technique for extracting these subscales is principal components analysis (PCA). In a previous study in PD patients [19], a factor solution of the BAI was not found by using PCA, which might be explained by the great heterogeneity of the investigated study population. In a previously conducted PCA by our research group, based on a large cohort of patients that were referred to our outpatient clinic for movement disorders, we found that the BAI encompasses one affective and four somatic factors [18]. A significant association between the symptoms of anxiety and depression was found, and severity of motor symptoms showed significant associations with the somatic (and not affective) factors of the BAI. Another study investigated the dimensionality of the BAI by principal axis factoring, and found one distinct PD motor subscale [12].

In the current study we aim to replicate the findings of Rutten et al. [18] in an independent sample of PD patients who were specifically referred for specialist neuropsychiatric evaluation. Using the same methodology in a different patient sample enables us to investigate the generalizability of the previous findings [20].

Methods

Subjects

The data used in this cross-sectional study were routinely collected at the Center for Neuropsychiatry in Parkinson's disease (CNP) of the Amsterdam University medical center, location VUmc in Amsterdam, the Netherlands. The CNP is a specialized outpatient department for the diagnosis and treatment of PD patients experiencing neuropsychiatric symptoms. Patients are referred to the CNP by neurologists, general practitioners and specialists in geriatric medicine. Data of 176 patients were collected between April 2014 and February 2018. Patients were included if they were previously diagnosed with idiopathic Parkinson's disease and provided written informed consent for their clinical data to be used in scientific research. Since several patients were included in both the previous and the current databases, we excluded overlapping patient data collected within five years after the data collection of Rutten et al. [18].

Measurements

Clinical and demographic characteristics

The Montreal Cognitive Assessment (MoCA) was used to screen the patient group for possible cognitive decline [21]. The United Parkinson Disease Rating Scale-III (UPDRS-III) score was used to assess the severity of motor symptoms [22]. The Beck Depression Inventory (BDI) was used to examine self-reported symptoms of depression [23]. The BDI cut-off score for clinically relevant symptoms of depression is 14 [24].

The patient's history of psychiatric diagnoses was recorded as well as the psychiatric diagnoses given after the diagnostic examination, which was done by clinical evaluation by the assessing psychiatrists (OvdH/SR). Due to the time-frame in which data was collected, both the Diagnostic and Statistical Manual of Mental Disorders (DSM-)IV and the DSM-5 were used [25].

Patient sex, age, time since PD diagnosis (e.g. disease duration), and the use of dopaminergic medication (0 = no, 1 = yes) were recorded.

Anxiety
The BAI is a self-report instrument that consists of 21 items, through which patients can report the symptoms of anxiety that they have experienced in the previous week. Items are scored on a 4-point Likert scale, which ranges from 0 (not at all) to 3 (severely), with a total score range from 0 to 63 [17]. The cut-off score used for clinically relevant anxiety in PD is > 12 [19].

Statistical analyses

All analyses were performed using SPSS Statistics 22 for Windows with a two-sided significance level of $p < 0.05$. The acceptability of missing values of the BAI and BDI was set to less than three missing items, i.e. 16.67%. If this criterion was not met, the patient's data was excluded from further analysis. Mean imputation was used for residual missing data of the BAI and BDI. Data were excluded pairwise when the total MoCA score and/or the total UPDRS-III score was not available since imputation was not considered to be reliable.

PCA was used to assess the dimensionality of the BAI. In PCA, items that share the most common explained variance cluster together in factors. In order to determine the number of factors that can be reliably extracted, the 'scree plot' criterion and the Guttman-Kaiser Eigenvalue greater-than-one rule were used. Oblimin rotation was used since it was expected that the different factors correlate with each other. The resulting factors of the BAI can be considered subscales of the BAI. The scores on these subscales were used in further analyses.

The associations between the BAI and its subscales, BDI, MoCA, and UPDRS-III were investigated by conducting multiple linear regression analyses. Assumptions of normality and homoscedasticity of residuals were checked. Multicollinearity was evaluated by calculating the variance inflation factor (VIF) and investigation of the correlation matrix.

In the first set of regression analyses, the total BAI score was the dependent variable. In the second set, the scores on the subscales of the BAI derived from the PCA were the dependent variables. The independent variables were the total score on the BDI, UPDRS-III, and MoCA. First, we investigated the association between the dependent and independent variables in an unadjusted model. Next, we adjusted the model stepwise for age and gender (model 1), use of dopaminergic medication (model 2), and the two other independent variables of interest, i.e. the BDI, MoCA, and UPDRS-III (model 3).

Results

Of the available patient sample of 176 patients, 48 patients were excluded due to >16.67% missing BAI-items. Of the remaining 128 patients, five patients were excluded due to overlap with the sample of Rutten et al. [18]. Finally, the total sample used in our analyses consisted of 123 patients.

Demographic and clinical characteristics

Demographic and clinical characteristics of the patient sample are shown in Table 1. Due to missing data on the UPDRS-III and unknown disease duration, 14 and 38 additional patients were excluded in these characteristics data, respectively. The majority of patients was male, mean age was 66.1 years. Patients had a mean UPDRS-III score of 27.3 and a mean MoCA score of 23.8, with 55.9% of patients scoring below the cut-off of 26 points, indicative of cognitive decline [26].

Half of the patients (49.6%) had sought treatment for psychiatric symptoms prior to receiving a PD diagnosis. Of this sub-population, 45.5% did so specifically for symptoms of anxiety. Currently, the vast majority of the patients (91.9%) received at least one psychiatric diagnosis.

Table 1. Clinical and demographic characteristics (N = 123)

	Mean	SD	Range
% Female	38.2		
Age	66.1	9.8	34-86
Disease duration (years) (n=85)	8.4	6.9	0-29
MoCA score	23.8	4.7	5-30
UPDRS-III score (n=109)	27.3	14.8	1-76
Total BAI score	20.3	11.4	0-55
Total BDI score	18.2	9.3	1-47
% Use dopaminergic medication	93.5		
% Treatment of psychiatric symptoms prior to PD diagnosis	49.6		

Anxiety

The mean BAI total score for this patient sample was 20.3 (± 11.4), and 77.4% of the patients had a BAI score higher than 12, indicating clinically relevant symptoms of anxiety. According to the psychiatrist's assessment, 65 patients (52.9% of the total sample) met DSM-IV or -5 criteria for an anxiety disorder.

Table 2. Psychiatric diagnoses as given by assessing psychiatrist (N = 123)

Diagnosis given (DSM-IV or –V)	%
No diagnosis	8.1
Anxiety disorders	52.9
Due to somatic disorder (PD)	41.5
Panic disorder	6.5
Generalized anxiety disorder	3.3
Social anxiety disorder	1.6
Depressive disorders	41.4
Due to somatic disorder (PD)	25.2
Persistent depressive disorder (dysthymia)	0.8
Major depressive disorder	15.4
Neurocognitive disorder	31.7
Other specified disruptive, impulse-control and conduct disorder*	16.3
Psychotic disorder	12.9
Sleep-wake disorder	15.4

** all patients fulfilling criteria for this DSM category had an impulse control disorder*

Of these 65 patients, 79.3% received at least one other psychiatric diagnosis. Depressive disorders were the most frequent occurring comorbidity, as they were diagnosed in 42.3% of patients with an anxiety disorder. Based on both BAI and BDI total scores, 62.4% of the patients had clinically relevant symptoms of both anxiety and depression.

Principal component analysis of the BAI

Examination of the scree-plot and the Eigenvalue greater than 1 rule suggested five factors. All BAI-items had a loading greater than 0.4 on at least one of the factors and therefore all items were included in the factor solution. No items had a loading greater than 0.4 on multiple factors.

The five extracted factors were considered subscales with the following labels; *affective, thermoregulation, cardiopulmonary, unsteadiness and 'undefined'*. The last factor included three items (i.e. dizzy/lightheaded, faint/lightheaded, and indigestion) that we could not clinically interpret as an evident subdomain of anxiety.

Therefore, we decided not to label this as a subscale and excluded it from further analyses. The factor solution explained a total of 64.6% of the variance, 59.1% excluding the last factor, with the *affective* subscale explaining 35.9% of the total

variance. Figure 1 shows the distribution of the BAI items over the five subscales, with the corresponding factor loadings.

Associations between anxiety, depression, cognitive and motor dysfunction

The residuals of both the total BAI score and subscales of the BAI had a positively skewed distribution, as shown by histograms. Normality was not improved after transformation of the data. Therefore, we used the original data for the analyses to maintain interpretability of results. Homoscedasticity and non-multicollinearity of the data was confirmed. The VIF ranged from 1.02 to 1.44 and the correlation matrix is displayed in supplementary table S1.

Table 3 shows the results of the multiple regression analyses with the BAI total score and scores on the subscales of the BAI as dependent variable. The final, adjusted models are displayed, including all independent variables in the associations with the dependent variables. The unadjusted and adjusted models can be found in Supplementary table S2.

As displayed in table 3, the BAI total score and the *affective* subscale of the BAI were both significantly associated with the BDI score. The BAI total and *affective* scores were negatively associated with the MoCA score. In the final adjusted model, the associations between the MoCA score and BAI total and *affective* scores were no longer statistically significant due to confounding by the BDI score. No other significant associations were found.

Discussion

In this study, we replicated the findings of our previous study [18] in an independent PD patient sample with neuropsychiatric symptoms necessitating referral to an expert neuropsychiatric outpatient clinic.

From the data collected from the current CNP patient sample, PCA uncovered four clinically interpretable factors, representing subscales of the BAI (*affective, thermoregulation, cardiopulmonary,* and *unsteadiness*). As in the results published by Rutten et al. [18], there was a partition of psychological and somatic symptom dimensions and the highest percentage of the variance was explained by the *affective* subscale. This demonstrates the generalizability to an independent PD sample and confirms the robustness of our results. While the *affective* and *thermoregulation*

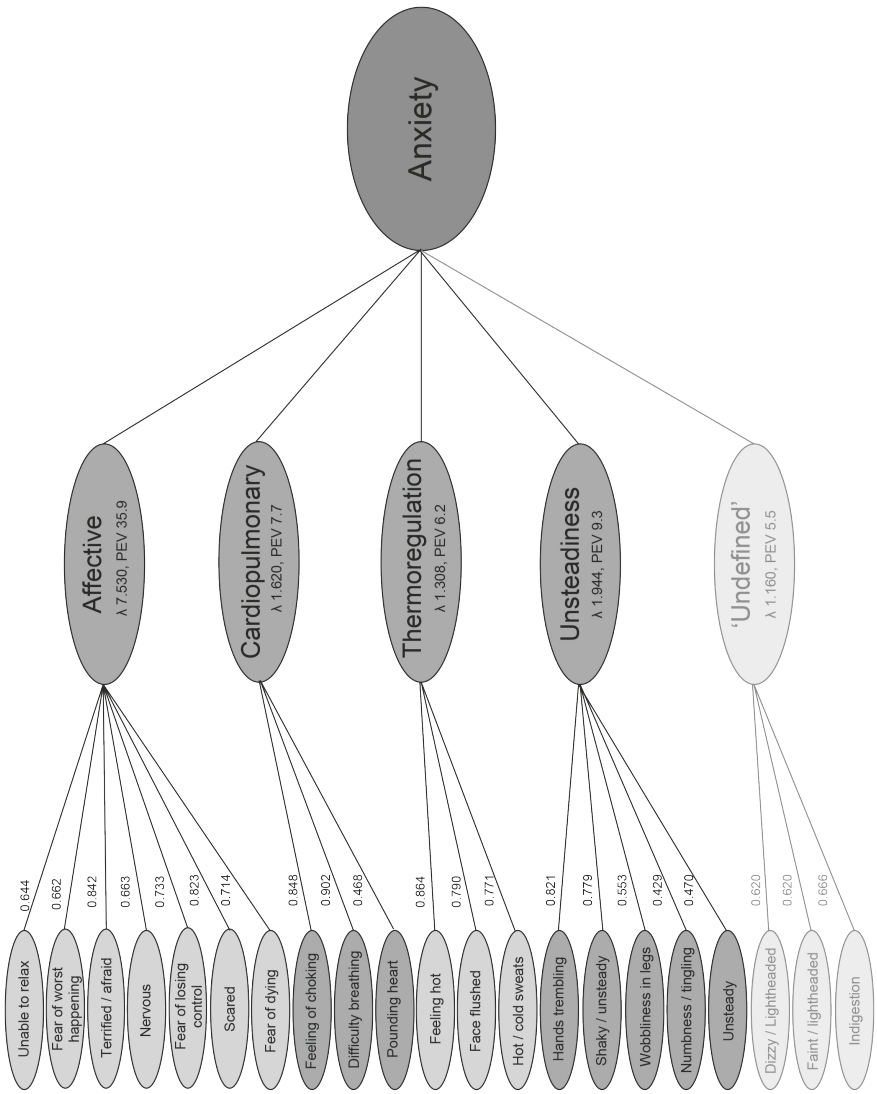

Fig. 1. Graphical display of the Principal Component Analysis results of the Beck Anxiety Inventory. Factor loadings, Eigenvalues (λ), and percentages of explained variance (PEV) are displayed.

Table 3. Results of multiple linear regression analyses of the BAI total score and score on subscales of the BAI with the BDI, SCOPA-AUT and UPDRS-III. Regression coefficients (B) with 95% confidence intervals (95%-CI of B), standardized regression coefficients (b) and significance (indicated with*) are displayed for the final model.

DEPENDENT VARIABLE → INDEPENDENT VARIABLE ↓	Total BAI score			Affective			Thermoregulation			Cardiopulmonary			Unsteadiness		
	B	95% CI of B	β	B	95% CI of B	β	B	95% CI of B	β	B	95% CI of B	β	B	95% CI of B	β
(constant)	11.915	-10.559 to 34.389		4.854	-4.602 to 14.310		3.154	-2.525 to 8.834		3.621	-.955 to 8.197		2.992	-5.719 to 11.704	
BDI	0.691	0.503 to 0.880	**0,569***	0.246	0.167 to 0.326	**0.503***	0.008	-.039 to 0.054	0.035	-.009	-.048 to 0.029	-.046	0.004	-.069 to 0.077	0.011
MoCA	-.339	-.786 to 0.108	-.141	-.177	-.365 to -.011	-.182	-.001	-.114 to 0.112	-.002	-.045	-.136 to 0.046	-.117	0.069	-.105 to 0.242	0.095
UPDRS-III	-.003	-.130 to 0.123	-.004	-.027	-.080 to 0.026	-.087	0.009	-.023 to 0.041	0.058	-.015	-.041 to 0.010	-.124	0.005	-.045 to 0.054	0.019
Gender	2.729	-.856 to 6.313	0.117	0.993	-.515 to 2.501	0.106	0.049	-.857 to 0.955	0.011	0.122	-.607 to 0.852	0.033	-.507	-1.896 to 0.882	-.072
Age	0.032	-.179 to 0.243	0.028	0.020	-.069 to 0.108	0.042	-.008	-.062 to 0.045	-.037	-.024	-0.067 to 0.019	-.131	0.023	-.058 to 0.105	0.067
PD MEDICATION	-2.074	-9.182 to 5.034	-.045	-.493	-3.483 to 2.498	-.027	-.855	-2.651 to 0.941	-.095	1.170	-.277 to 2.618	0.158	0.018	-2.737 to 2.773	0.001
R^2	0.402			0.349			0.013			0.047			0.012		

* = *p<0.001*

subscales were exact replications, the *cardiopulmonary* and *unsteadiness* subscales showed a slightly different composition to the previously found subscales *hypotension, hyperventilation,* and *trembling*.

The BAI total score and the BAI *affective* subscale score were significantly associated with the BDI score. This high correlation between the BAI and the BDI was also reported in the previous study [18]. This suggests a high co-occurrence of anxiety and depressive symptoms [5], as is also supported by Zhu and colleagues [4], who found that up to 70% of anxious PD patients also suffer from depression. The BAI total score and BAI *affective* subscale score were also significantly associated with the MoCA score. However, in the final adjusted model, this association was no longer significant due to confounding by the BDI score, explained by the high correlation between the BAI and BDI (see table S1 for Pearson's correlations between BAI, BDI, UPDRS-III, MoCA, and age). In contrast to the previous study [18], no significant associations between somatic subscales and motor symptoms were found. The current patient sample showed more neuropsychiatric symptoms, but had a similar degree of motor dysfunction (see supplementary table S3 for the independent samples t-tests results of the comparison of the sample characteristics). The slightly different distribution of BAI-items over the somatic subscales might explain the absence of the associations with motor symptoms in the current sample.

Based on the BAI total score, 77.4% of the current patient sample showed clinically relevant anxiety. However, only 52.9% of patients received a formal DSM-IV or -5 anxiety diagnosis from the assessing psychiatrist. This could be due to symptom overlap and high co-occurrence with depression, in which case a depressive disorder might be more fitting with the clinical presentation in some cases. In addition, anxiety symptoms can occur in the context of other psychiatric disorders, such as psychosis, dementia, and dopamine dysregulation syndrome. Besides neuropsychiatric comorbidity, anxiety in PD often has an atypical presentation, leading to the symptoms not fitting into the disorders listed in DSM-IV and -5 [27]. Another possible explanation is that the severity of anxiety may be overestimated by the BAI [16], since motor and autonomic symptoms of PD could have inflated the scores on this self-report instrument. Nevertheless, it must also be kept in mind that the same motor and autonomic symptoms can mask anxiety symptoms during clinical evaluation.

The disentanglement of anxiety from motor symptoms in PD is both scientifically and clinically challenging [12, 16]. In our previous study [18], we found that the *affective* subscale was the only factor not associated with autonomic dysfunction,

as measured with the Scales for Outcomes in Parkinson's disease – Autonomic dysfunctions (SCOPA-AUT), and motor dysfunction as measured with the UPDRS-III. This is of clinical importance since it could indicate that certain items of the BAI should be weighted more heavily when screening for clinically relevant anxiety in PD. Therefore, in a post-hoc analysis, we investigated whether the score on the *affective* subscale of the BAI alone was better in predicting an anxiety disorder diagnosis given by a psychiatrist compared to the total score of the BAI. We calculated the area under the Receiver Operating Characteristic (ROC) curve of both the BAI total score and the *affective* subscale of the BAI in relation to an anxiety disorder diagnosis (yes or no). The area under the ROC curve of the BAI total score was 0.77 (sd = 0.04, $p < 0.001$). The *affective* subscale of the BAI showed an area under the ROC curve of 0.75 (sd = 0.05, $p < 0.001$). We can thus conclude that the BAI total score and the BAI *affective* subscale score have similar power in predicting an anxiety disorder diagnosis given by a psychiatrist in this PD patient sample. Using only the score on the *affective* subscale (7 items) in the prediction of an anxiety disorder diagnosis saves time and might be more practical compared to using the total BAI (21 items). In addition, this subscale might be considered as containing psychological and non-episodic anxiety items, which suspends the discussion about how to interpret the somatic BAI-items.

To evaluate the *affective* subscale further, comparison with other screening options for anxiety in PD is useful. The Movement Disorder Association currently does not recommend one specific anxiety screening instrument (latest published research from 2008 [28]), but does recommend the non-motor rating scale (the MDS-NMS) in which four questions about anxiety are included [29]. Two of those questions represent two items of the *affective* subscale of the BAI, the other two ask about panic attacks and social anxiety. Another screening tool for anxiety, the Parkinson Anxiety Scale (PAS), is a self-report questionnaire that includes items specifically for non-episodic anxiety and avoidance behavior [30]. The PAS excludes almost all somatic symptoms of anxiety, except for panic related symptoms (e.g. shortness of breath and heart palpitations). All non-episodic anxiety items of the PAS are comparable to the items that clustered together in the *affective* subscale.

This study has some limitations. The BAI focusses mostly on episodic anxiety, i.e. symptoms of panic disorder, while non-episodic anxiety, like in generalized anxiety disorder, is also common in PD. Unfortunately, autonomic dysfunction was not measured in the current patient sample, restricting the investigation of its associations with the (subscales of the) BAI. In terms of psychiatric diagnoses, this patient sample was not assessed with a structured clinical interview, to

systematically check diagnostic criteria for all DSM diagnoses. Such structured clinical interviews, however, also risk overdiagnosis due to anxiety features being considered as part of a primary anxiety diagnosis, instead of secondary to another psychiatric diagnosis or PD-related symptoms of motor or autonomic failure, as can be expected in PD patients.

A major strength of this study is that we investigated a sample of PD patients who were assessed by two psychiatrists who are specialized in diagnosing anxiety in the context of motor and autonomic symptoms in PD patients. We successfully replicated the main findings by Rutten et al. [18], which makes these results more reliable and generalizable.

Conclusions

In conclusion, anxiety in PD is a complex construct due to symptom overlap and interactions with motor and autonomic features of the disease. The 7-item *affective* subscale of the BAI shows potential as a screening tool for non-episodic anxiety in PD. It is recommended to evaluate anxiety symptoms in the context of other PD symptoms, including motor, autonomic, and other (neuro)psychiatric symptoms.

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Supplementary material Chapter 3

Table S1. Matrix of the Pearson's correlation coefficients (*r*) for the BAI, BDI, UPDRS-III, MoCA, and age.

	BAI	BDI	UPDRS-III	MoCA	Age
BAI	1.000	0.599**	0.015	-0.248**	0.123
BDI	0.599**	1.000	-0.44	-0.141	0.27
UPDRS-III	0.015	-0.44	1.000	-0.319**	0.306**
MoCA	-0.248**	-0.141	-0.319**	1.000	-0.519**
Age	0.123	0.27	0.306**	-0.519**	1.000

***p-value < 0.01 (2-tailed)*
Abbreviations: BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; UPDRS-III = Unified Parkinson's Disease Rating Sccale – part three (motor examination); MoCA = Montreal Cognitive Assessment.

Table S2: Results of multiple linear regression analysis association BAI total score and score on subscales of the BAI with BDI, MoCA and UPDRS-III. All associations are adjusted for covariates in three consecutive models. Regression coefficients (B) and 95% confidence intervals (95%-CI) and significance (p-values, indicated with *) are displayed, as well as information on confounding covariates (Ad 1).

		Crude model		Model 1		Model 2		Model 3	
B		**95%-CI**	**B**	**95%-CI**	**B**	**95%-CI**	**B**	**95%-CI**	
BAI total score									
BDI		0.727***	0.541 – 0.913	0.709***	0.524 – 0.895	0.714***	0.528 – 0.900	0.691***	0.503 – 0.880
MoCA	1	-.597**	-1.044 – -.150	-.580*	-1.101 – -.060	-.580*	-1.106 – -.053	-.339	-.786 – 0.108
UPDRS-III		0.012	-.136 – 0.159	-.009	-.162 – 0.144	-.008	-.162 – 0.146	-.003	-.130 – 0.123
Subscale Affective									
BDI		0.266***	0.187 – 0.344	0.259***	0.180 – 0.337	0.260***	0.181 – 0.339	0.246***	0.167 – 0.326
MoCA	1	-.252**	-.432 – -.072	-.244*	-.453 – -.034	-.244*	-.456 – -.032	-.177	-.365 – 0.011
UPDRS-III	1	-.014	-.073 – 0.046	-.026	-.087 – 0.036	-.025	-.087 – 0.037	-.027	-.080 – 0.026
Subscale Thermoregulation									
BDI		0.007	-.039 – 0.052	0.007	-.040 – 0.053	0.008	-.039 – 0.054	0.008	-.039 – 0.056
MoCA		-.005	-.096 – 0.086	-.015	-.123 – 0.092	-.010	-.118 – 0.098	-.001	-.114 – 0.112
UPDRS-III		0.005	-.024 – 0.034	0.007	-.023 – 0.038	0.009	-.022 – 0.039	0.009	-.023 – 0.041
Subscale Cardiopulmonary									
BDI		-.003	-.040 – 0.035	-.003	-.041 – 0.035	-.005	-.043 – 0.033	-.009	-.048 – 0.029
MoCA		0.000	-.074 – 0.074	-.024	-.111 – 0.064	-.031	-.118 – 0.057	-.045	-.136 – 0.046
UPDRS-III		-.014	-.037 – 0.010	-.011	-.036 – 0.014	-.012	-.037 – 0.013	-.015	-.041 – 0.010
Subscale Unsteadiness									
BDI		-.003	-.073 – 0.067	0.000	-.071 – 0.071	-.001	-.072 – 0.071	0.004	-.069 – 0.077

Table S2: Continued.

	Crude model		Model 1		Model 2		Model 3	
B	**95%-CI**	**B**	**95%-CI**	**B**	**95%-CI**	**B**	**95%-CI**	
MoCA	0.043	-.096 – 0.182	0.064	-.099 – 0.228	0.064	-.102 – 0.229	0.069	-.105 – 0.242
UPDRS-III	0.003	-.042 – 0.047	0.000	-.047 – 0.048	0.000	-.047 – 0.048	0.005	-.045 – 0.054

** p-value <0.05, ** p-value < 0.01, *** p-value < 0.001*

Model 1: adjustment for age and gender
Model 2: adjustment for age, gender, and use of dopaminergic medication
Model 3: adjustment for age, gender, use of dopaminergic medication, and score on the BDI and/or MoCA and/or UPDRS-III score

Ad 1: confounding by the BDI score.
Abbreviations: BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; UPDRS-III = Unified Parkinson's Disease Rating Sccale – part three (motor examination); MoCA = Montreal Cognitive Assessment.

Table S3. Independent samples t-tests results of the comparison of the sample characteristics between the current and the previous [18] patient sample.

Outcome measure	**Mean (sd) Rutten et al. [18]**	**Mean (sd) current sample**	**Difference in mean (CI)**	**t-value** (df=415)	**Significance**
BAI	14.2 (9.8)	20.3 (11.4)	6.1 (3.94 – 8.26)	5.58	P<0.001
BDI	11.4 (8.0)	18.2 (9.3)	6.8 (5.03 – 8.57)	7.63	P<0.001
Age	64.5 (10.3)	66.1 (9.8)	1.6 (-.53 – 3.73)	1.48	ns
UPDRS-III (n=109)	25.8 (12.3)	27.3 (14.8)	1.5 (-1.31 – 4.31)	1.06	ns
Disease duration (n=85)	5.1 (5.6)	8.4 (6.9)	3.3 (1.94 – 4.66)	4.81	P<0.001

Abbreviations: BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; UPDRS-III = Unified Parkinson's Disease Rating Sccale – part three (motor examination); MoCA = Montreal Cognitive Assessment, n = amount of patients; sd = standard deviation; CI = Confidence Interval; df = degrees of freedom; ns = nonsignificant.

4

Symptom connections in anxious versus low-anxious Parkinson's disease patients: an explorative network study

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In preparation

Abstract

Introduction: Approximately 45% of patients with Parkinson's disease (PD) experience clinically relevant anxiety. Anxiety and motor symptoms are highly intertwined and have reciprocal influences. We investigated the associations between motor and anxiety symptoms in patients with high levels of anxiety compared to patients with low levels of anxiety.

Methods: Data were collected during routine clinical assessments at the outpatient clinic for movement disorders. Motor symptoms were measured with the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III). A cut-off score of 12 on the Beck Anxiety Inventory (BAI) was used to divide patients into high-anxious versus low-anxious patients. Explorative network analyses and a network comparison test were used to investigate the partial correlations between items of the UPDRS-III and the BAI, and to statistically compare network architecture between the two patient groups.

Results: 316 PD patients were included in the high-anxiety group, versus 253 in the low-anxiety group. The high-anxiety group showed significantly worse motor and cognitive function, a higher age, and included more female patients. The high-anxiety group had a higher global strength compared with the low-anxiety group ($S=7.33$, $p<0.001$). We found no statistically significant differences in strength of the connections between motor and anxiety symptoms between both groups.

Conclusion: In spite of clear differences in demographic and clinical profile, we did not find differences in the associations between motor and anxiety symptoms, comparing high-anxious to low-anxious PD patients. Since associations between motor and anxiety symptoms are apparent in both groups, this shows that these symptoms are associated, even when patients have no to mild anxiety symptoms. These results need to be interpreted with caution and warrant replication in a bigger sample.

Introduction

Parkinson's disease (PD) is classified as a movement disorder but is also associated with non-motor symptoms. These include neuropsychiatric symptoms such as depression, anxiety, cognitive decline, and psychotic experiences [1, 2]. A large international study of both motor and non-motor symptoms in 411 PD patients showed that non-motor symptoms have, as a whole, a greater impact on health related quality of life compared to motor symptoms [3]. Martinez-Martin and colleagues [3] assessed 545 patients and showed that 98.4% of PD patients reported one or more non-motor symptoms. Depression and anxiety symptoms were in the top three of most prevalent non-motor symptoms. In PD, motor and non-motor symptoms are highly intertwined and show reciprocal influences [3-7]. About 75% of patients with fluctuations in motor symptoms experience mood and/or anxiety fluctuations in parallel [8]. For example, PD patients can experience anxiety and panic attacks during an 'off' phase, in which motor symptoms are re-occurring [5].

We previously performed a factor analysis on the Beck Anxiety Inventory (BAI) to investigate the different symptom dimensions of anxiety in PD patients [9]. We uncovered four 'somatic' (containing mostly physical symptoms) and one 'affective' dimension (containing purely emotional and cognitive anxiety symptoms). A regression analysis demonstrated that depressive symptoms were significantly associated with the 'affective' dimension of the BAI, motor and autonomic symptoms were significantly related to the 'somatic' dimensions of the BAI. The main results of this study were replicated in an independent sample of PD patients that had been referred for specialist psychiatric evaluation (under review). These study findings demonstrate that some aspects of anxiety in PD are strongly connected to the motor symptoms of the disease. However, it is yet unclear which specific characteristics of anxiety are responsible for the significant associations with motor symptoms. Also, it remains to be determined whether PD patients with high levels of anxiety show stronger connections between anxiety and motor symptoms compared to PD patients with low levels of anxiety.

An approach that is useful for investigating associations between symptoms is network analysis [10]. With this method, it is possible to explore and visualize partial correlations between symptoms. This method can establish which symptoms are correlated (strongly or weakly, positively or negatively) and can be used to compare symptom network architectures between groups [10]. A network analysis approaches the multifaceted and complex nature of the relationships between anxiety and motor symptoms in PD by calculating the associations between

symptoms in the context of all other symptoms that are included in the network. Using this method, van der Velden and colleagues [11] investigated the influence of motor and non-motor symptoms using time-series data of one PD patient and showed that higher anxiety scores were longitudinally associated with increased rigidity and tremor [11].

To gain more insight in the associations between individual motor and anxiety symptoms cross-sectionally, and to investigate whether these associations depend on the presence of clinically significant symptoms of anxiety, we performed a network comparison analysis on PD patients with high levels of anxiety versus PD patients with low levels of anxiety. We expected a significant difference between high-anxious versus low-anxious PD patients in symptom network architecture, with the high-anxiety group showing significantly stronger associations between motor and anxiety symptoms than the low-anxiety group.

Methods

Subjects

Data were collected during routine clinical assessments at the outpatient clinic for movement disorders of the Amsterdam University Medical Center (Amsterdam UMC), location VUmc, in Amsterdam, the Netherlands, between May 2008 and May 2018. In this period, 649 PD patients were assessed. Patients were clinically diagnosed with idiopathic PD according to the United Kingdom PD Society Brain Bank criteria. A cutoff of 12 on the BAI was used to divide the total patient sample into a high-anxiety and a low-anxiety group [12].

All included patients gave written informed consent to use their clinical data for scientific purposes. Patients with missing data on the motor or anxiety outcome measures were excluded.

Measurements

To describe the patient groups, age and gender were recorded, as well as total scores on the Mini Mental State Examination (MMSE), and section III of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Both the MMSE and UPDRS-III were assessed by a neurologist in training.

Scoring of motor symptoms, using the UPDRS-III [16], was performed on a four-point Likert scale, ranging from 0 to 3 per item. The UPDRS-III contains 39 items and a higher score represents more severe motor symptoms.

Symptoms of anxiety were measured with the BAI. The BAI is a 21-item self-report instrument asking for symptoms of anxiety over the past week [13]. Patients answer on a four-point Likert scale, ranging from 0 (not at all) to 3 (severely) per item.

Statistical analyses

The analyses were performed in the statistical program *R* (version 3.6.1, developed by the R Core Team, 2015). Differences in descriptive measures were investigated using independent t-tests or Mann-Whitney U tests, and chi-square tests where appropriate.

The package *qgraph* was used to perform the network analyses and visualizations [14]. Since it concerned ordinal data, a Gaussian Graphical Model with LASSO regularization was applied [15]. The tuning parameter, *gamma*, was set at 0.5 to obtain a network structure in which few associations are required to parsimoniously explain the covariance among the variables, reducing false positive associations [15]. Associations within a network are represented by color-coded lines between symptoms, which are green for positive associations and red for negative associations. The thicker the lines, the stronger the association between two symptoms.

The Network Comparison Test (NCT) was used to investigate differences in associations between motor and anxiety symptoms between the two patient groups [16]. From the NCT, two types of measures were extracted. The first measure concerns global strength, which represents the overall connectedness between all symptoms within the network. A higher global strength results from more and stronger associations between symptoms. Second, all associations between separate symptoms are calculated individually, and can be compared between the two patient group networks. The Holm-Bonferroni method was used to correct for multiple comparisons.

To investigate the accuracy and stability of our network estimates, a bootstrap procedure was applied. Using the R package *bootnet*, a number of 100 bootstrap samples with the nonparametric method was used [15]. The sampling distribution was then visually inspected.

It is important to notice that, considering this statistical method, our sample sizes are small and these analyses should therefore be considered explorative [17].

Results

Subjects

Of the 649 assessed PD patients, 80 were excluded due to missing data. Using the cut-off score of 12 on the BAI, 316 patients were assigned to the high-anxiety group and 253 patients were assigned to the low-anxiety group.

We initially matched the two patient groups on age and sex using the *matchit* package, since the NCT is most reliable when two networks of equal sample size are compared. However, this resulted in very small sample sizes (n=139 per group) with still significant differences in age and sex between the groups. To retain the highest possible power we decided to perform our analyses with the largest, unmatched sample sizes.

Descriptive statistics

Descriptive and clinical measures of the two patient groups are displayed in table 1. The high-anxiety group was older, included more females, and showed significantly higher severity of motor impairment and cognitive decline. Since we divided the two groups based on anxiety level, there was also an expected difference in severity of anxiety symptoms.

Table 1. Characteristics of the anxious and non-anxious PD patient groups.

	Anxious	Non-anxious
Mean		
N	316	253
Age (sd)	67.3 (9.8)*	65.2 (11.0)*
Sex	44% female**	33% female**
BAI total (sd)	25.5 (10.1)***	6.7 (3.5)***
UPDRS-III total (sd)	30.4 (20.2)***	23.0 (11.4)***
MMSE total (sd)	26.7 (3.6)***	27.7 (3.2)***

** p<0.05; ** p<0.01; *** p<0.001*
sd = standard deviation; BAI = Beck Anxiety Inventory; UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini Mental State Examination

Network comparison analysis

The networks for both groups are displayed in figure 1. In total, the network represents the partial correlations between 50 items (i.e. motor and anxiety symptoms) and since it concerns a parsimonious network, all visual correlations are considered relevant. The network architecture of both the high-anxiety and low-anxiety group shows clustering of motor symptoms (i.e. UPDRS-III items) on the left side and clustering of anxiety symptoms (i.e. BAI items) on the right side. Resting tremor as well as action tremor items are somewhat separated from the rest of the UPDRS-III items. The symptoms within the networks of both patient groups are mainly positively correlated, which is represented by the green connective lines.

There is a significant difference between the high-anxiety and low-anxiety patient group networks in global strength (S=7.33, p<0.001), with the high-anxiety group showing higher global strength (20.16) compared to the low-anxiety group (12.83). This difference is mostly driven by the higher global strength (i.e. more and stronger connections) amongst the BAI items, as can be seen in figure 1. Also, the connections between the UPDRS-III items appear stronger in the high-anxiety patient group.

Explorative visual inspection of the specific connections between motor and anxiety symptoms shows correlations between BAI item 12 (i.e. trembling hands) and resting tremor items of the UPDRS-III. Also, BAI item 8 (i.e. unsteadiness) is associated with UPDRS-III items related to gait and posture. We found no statistically significant differences between the two patient groups concerning correlations between the motor and anxiety items.

Concerning the stability of the networks, bootstrapped confidence intervals are wide (figures S1 and S2 in the supplementary materials) in both patient group networks.

Discussion

We investigated the differences in symptom network architecture focusing on the connections between motor and anxiety symptoms in PD patients with high levels of anxiety versus PD patients with low levels of anxiety.

The high-anxious compared to the low-anxious PD group networks differed in global strength. This was expected, since we selected the groups on the amount and severity of anxiety symptoms, resulting in more and stronger connections especially amongst the BAI items of the high-anxiety group network. Previous research

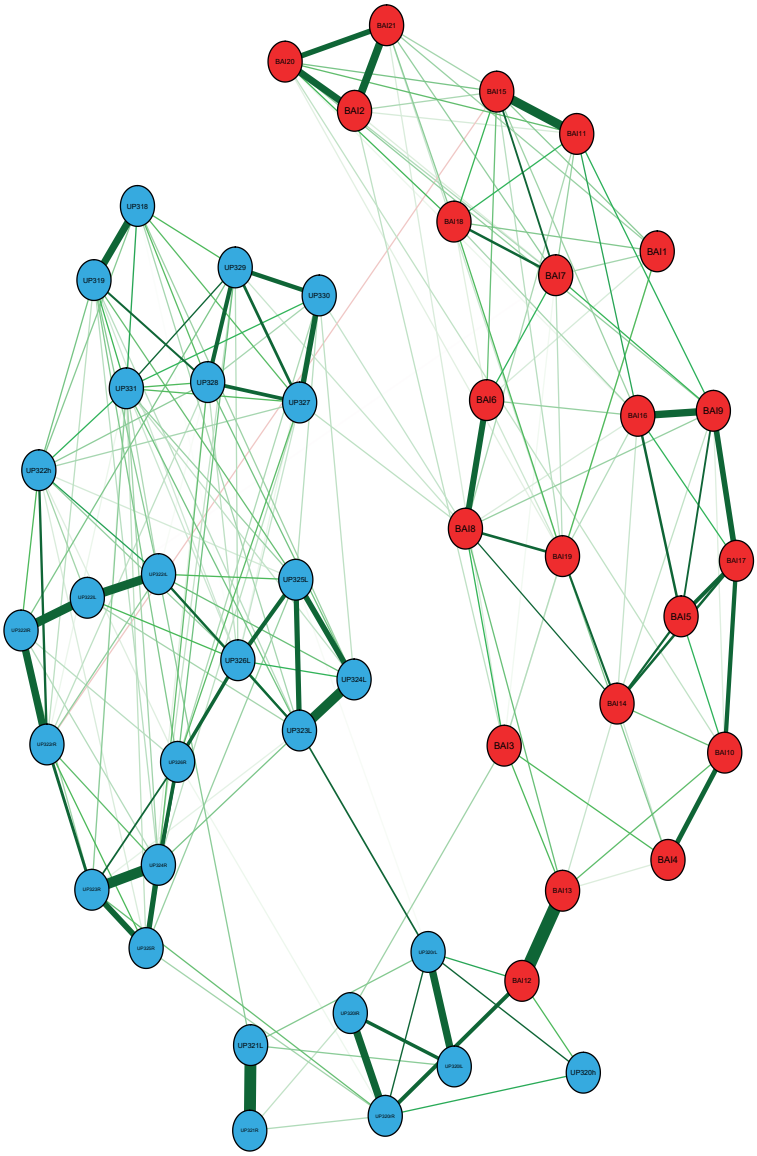

Figure 1a. Network analysis graphs. High-anxious PD patient group. The blue circles represent the motor symptoms as measured with the UPDRS-III, the red circles represent the anxiety symptoms as measured with the BAI.

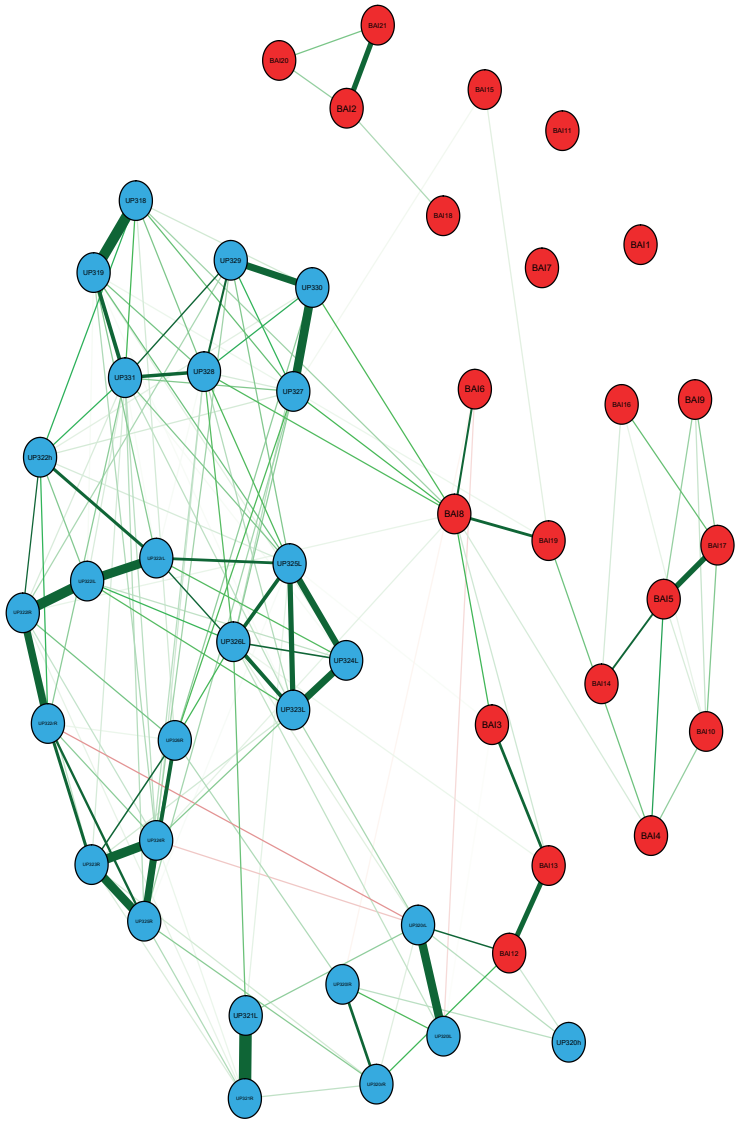

Figure 1b. Network analysis graphs. Low-anxious PD patient group. The blue circles represent the motor symptoms as measured with the UPDRS-III, the red circles represent the anxiety symptoms as measured with the BAI.

showed that higher anxiety levels are associated with more motor disability. The presence of more and stronger connections amongst the UPDRS-III items in the high-anxiety group network visually represent this, and contribute to the difference in global strength [3-5, 7, 8].

Visual inspection shows that BAI items 12 and 8 (trembling hands and unsteadiness, respectively) are connected with UPDRS-III items related to tremor, gait, and posture (see figure 1) in both patient groups. In contrast to our hypothesis that connections between motor and anxiety symptoms are stronger in PD patients with more severe anxiety, these connections do not differ in strength between the high-anxious and low-anxious PD groups. As these connections between symptoms appear to be present independent of anxiety level, a possible explanation for the similar connectedness between UPDRS-III and BAI items, is that they both quantify the same symptom, independent of its etiology. For example, BAI item 12 (trembling hands) measures a tremor in the context of anxiety, and UPDRS-III item 20 (resting tremor) measures a tremor in the context of PD symptomatology. However, whether they often appear together as separate symptoms or appear to measure one and the same symptom independent of its etiology cannot be tested here and is therefore speculative [17].

We found significant differences in descriptive and clinical characteristics between the patient groups. The high-anxiety group was older, included more females, and showed significantly more severe motor impairment and cognitive decline. The group difference in cognitive functioning is in line with what is seen in clinical practice. In general, PD patients with cognitive dysfunction are more anxious [18, 19]. The group difference in gender distribution is also in line with clinical practice and previous research, which shows that females show higher levels of anxiety compared to men [20, 21]. In spite of these clear differences in clinical profile, the connections between the motor and anxiety items were similar. This indicates that in this cross-sectional dataset certain motor and anxiety symptoms are intertwined independently of anxiety level and these symptoms are therefore important in the differential diagnosis of anxiety in PD. For example, when motor symptoms are very much apparent, anxiety symptoms might also be more apparent. When these anxiety symptoms mostly include items that appear to represent motor symptoms (such as BAI-items 8 and 12), patients might not be particularly anxious and treatment should be focused more on the motor symptoms.

Methodological considerations

Our initial plan to match the two patient groups on age and sex resulted in small sample sizes (n=139) without solving the differences in demographic and clinical variables. We therefore decided to perform our analyses with the largest sample sizes to retain the highest possible power. In network analysis, it is yet to be determined what is considered a satisfactory sample size [17]. It is suggested to perform network analysis on the largest samples since the networks are then estimated more accurately [15]. Relatively small sample sizes are a well-known issue in clinical research and with this it is considered challenging to gain an accurate estimation of a network [15], which was also the case in the present study. Both the low-anxious and high-anxious patient group showed an instable network, represented by the wide bootstrapped confidence intervals (figure 2), which limited us to draw reliable conclusions. In addition, we selected the patient groups on a total score of a questionnaire that was also directly represented as symptoms in the networks, which might have increased false positive associations known as Berkson's bias [22]. To avoid false positive results as much as possible, we conducted tuned analyses to gain parsimonious networks, and we corrected for multiple comparisons.

Obviously, the symptoms in our network are dependent on the items from the data sources (i.e. clinical assessments or questionnaires) on which they are based. Our network might therefore never be 'complete' (i.e. include all symptoms of the participating patients) and can involve different items that might measure the same symptoms, as is also discussed more in depth in the previous section. In addition, there might be other variables that influence the associations between items that were not accounted for, such as within-person variability and use of medication.

We studied motor an anxiety symptoms in PD as static measures using a cross-sectional approach. Therefore, we were not able to determine how these symptoms interact over time, as is especially relevant in the context of response fluctuations during the day [6, 11]. Network analysis may be very useful to visualize fluctuations of motor, autonomic and neuropsychiatric symptoms over time, using high-frequent individual time-series data from ecological monitoring assessment tools. It would be interesting to apply this statistical method to these response fluctuations and investigate the interactions between motor and anxiety symptoms more in depth. This also enables the study of direct effects of medication and environmental factors on the network architecture over time.

Conclusion

In this explorative network comparison analysis, we found a higher global strength in the high-anxious PD patients. No differences were found in the associations between motor and anxiety symptoms in high-anxiety versus low-anxiety PD patient groups. The two groups differed in multiple descriptive and clinical characteristics, which is representative for clinical practice and indicates that specific motor and anxiety symptoms are intertwined independent of anxiety level. Due to the small sample sizes, instability of the network structures, and possible Berkson's bias, these results need to be interpreted with caution. Further research is necessary to replicate in an independent bigger sample and to understand network architecture characteristics related to response fluctuations over time.

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Supplementary material Chapter 4

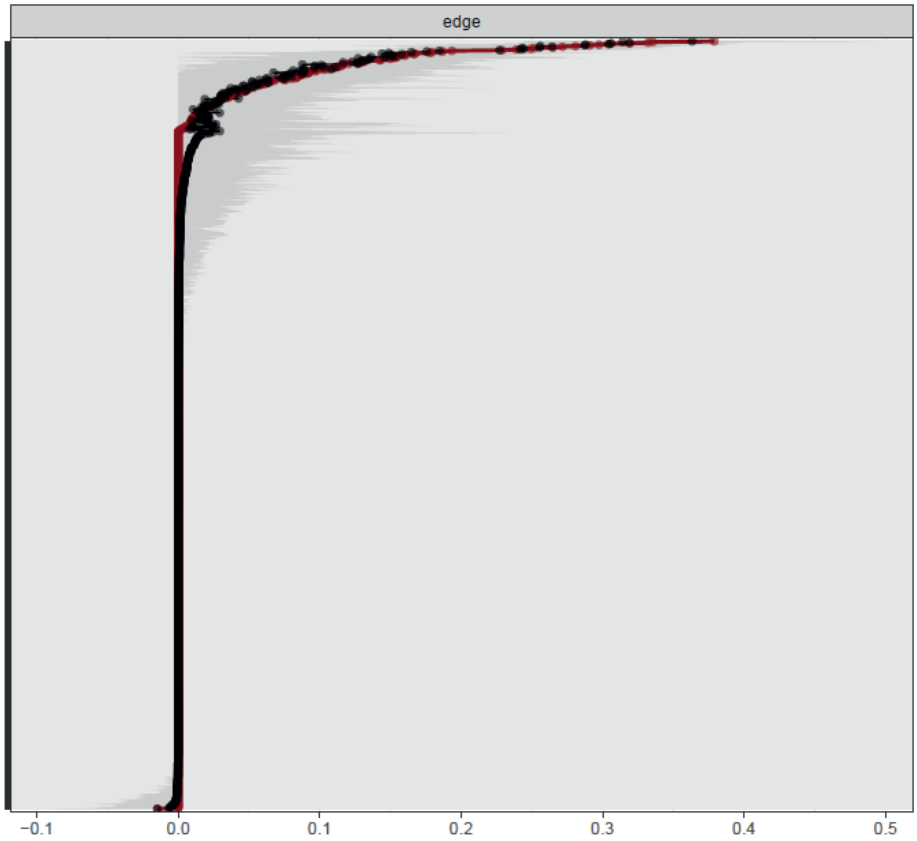

Figure S1. Bootstrapped means with confidence intervals of the strengths of the associations between symptoms in the low-anxiety patient group.

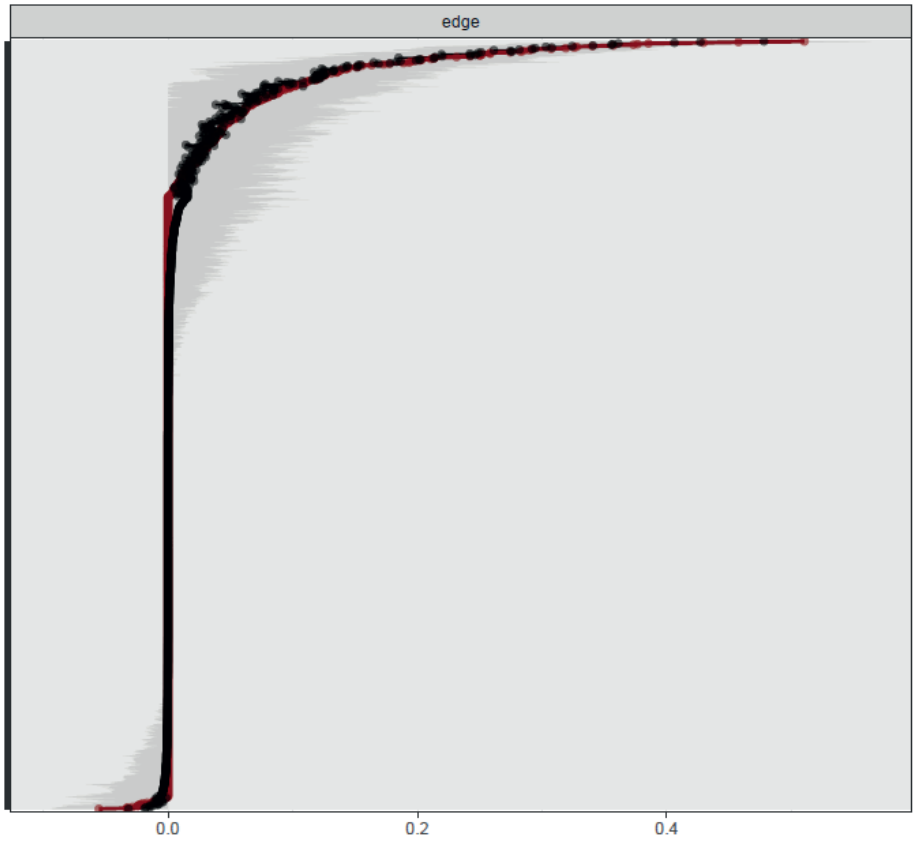

Figure S2. Bootstrapped means with confidence intervals of the strengths of the associations between symptoms in the high-anxiety patient group.

5

The association between Freezing of Gait, Fear of Falling and Anxiety in Parkinson's disease: a longitudinal analysis

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Abstract

Aims: We studied the longitudinal associations between Freezing of Gait (FoG), Fear of Falling (FoF) and anxiety, and how these associations are influenced by confounding factors.

Materials & methods: We analysed longitudinal motor and non-motor measurements from 153 Parkinson's disease (PD) patients. Possible confounding factors were divided into three subgroups: demographics, disease characteristics, medication use and adverse effects of medication.

Results: All crude associations between FoG, FoF and anxiety were significant and remained so after adjusting for confounders. When analysing FoF and anxiety together as independent variables, the association between FoG and FoF remained, and the association between FoG and anxiety diminished.

Conclusions: We confirm the complex interactions between motor and non-motor symptoms in PD, and plead for a multidisciplinary approach.

Introduction

Motor features, such as tremor, bradykinesia, hyperkinesia, rigidity, and gait disturbance have been the main focus in clinical management in Parkinson's disease (PD) for a long time. However, in the last decades, there is increasing awareness of the high prevalence and daily impact of non-motor symptoms, such as anxiety [1, 2]. More recently, reciprocal interactions between motor and non-motor symptoms are being investigated [2-4], leading to multidisciplinary treatment approaches [5].

One of the most disabling motor features of PD is freezing of gait (FoG), an episodic disturbance of gait pattern that affects up to 60% of PD patients, where they report feeling stuck or glued to the floor [6]. Giladi et al. [7] define FoG as a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk, including episodes in which the patient cannot initiate gait and arrests in forward progression during walking ("turn" and "destination" hesitation), as well as episodes of shuffling forward with steps that are millimetres to several centimetres in length. FoG severely affects quality of life and daily functioning and can result in falls and injuries [8, 9].

In clinical observations, the motor feature FoG is often accompanied by non-motor features such as fear of falling (FoF) [6], and cross-sectional studies suggest they may aggravate each other [3, 4]. FoF can be described as a lasting patients' loss of confidence in balance abilities [10]. With an estimated prevalence in PD of 35-59%, FoF is a permanent health concern inducing avoidance and restriction of activities and social life with a significant impact on the patient's independence [11].

Anxiety is another non-motor feature of PD which also contributes to reduced quality of life [12]. Anxiety has only recently received attention in the PD literature, despite the estimation that up to 40% of all PD patients experience clinically significant anxiety symptoms [13-15]. It occurs in various forms, such as social phobia, panic disorder, general anxiety disorder (GAD) and anxiety related to medication-induced fluctuations such as wearing-off [13, 16]. Studies about the association between FoF and anxiety in PD is scarce, however, anxiety has been described as a predictor of avoidance behaviour in PD patients with FoF [17].

The interaction between FoG and anxiety has been described in clinical practice as a vicious cycle, where anticipation of a FoG episode can trigger an experience of panic and the resulting increase in anxiety symptoms can in turn, trigger or exacerbate FoG [2, 18]. Recent experimental research supports the notion that anxiety is an

important contributor to FoG [3]. In addition, recent studies in PD suggest a PD-associated neurobiological susceptibility to anxiety [19, 20] and involvement of serotonergic [21], GABA-ergic and glutamatergic systems [22], in addition to the dopaminergic circuits.

Thus far, studies have focused on the cross-sectional association between FoG, FoF and anxiety. Longitudinal study designs take the levels of FoG, FoF and anxiety at onset into account, as well as the interaction between these symptoms over time. Therefore, a longitudinal study is more likely to investigate reciprocal associations between these symptoms. Moreover, other demographic and clinical factors may be more accurately reflected than a cross-sectional study by virtue of its scope.

The aim of this research was to study the longitudinal associations between FoG, FoF and anxiety, and how these associations are influenced by confounding factors such as demographics, disease characteristics, medication and adverse effects of medication. These results can guide professionals in order to identify and advise patients along the line of therapy, and to optimize diagnostic and treatment decisions.

Methods

Longitudinal data from the RESCUE trial (Rehabilitation in Parkinson's disease: Strategies for Cueing) was used. RESCUE was an observer-blinded, randomized, clinical trial with a crossover design, to evaluate the effects of home/based cueing training on gait and related activity in 153 PD patients [23, 24]. We refer to the study of Nieuwboer and colleagues [24] for the inclusion and exclusion criteria.

Study design

Subjects were randomly allocated to an early or late intervention group by an independent person not involved in the study. The early intervention group (n = 76) received a 3 week home cueing program using a prototype cueing device, followed by 3 weeks without training. The late intervention group (n = 77) underwent the same intervention after a three week waiting list period. After the initial 6 weeks, both groups had a 6 week follow-up without training. Outcome measures included motor impairment scores, questionnaires and physical activities, and were measured every 3 weeks by blinded researchers [23-25]. In addition to the outcome measures, demographic and disease related measures were assessed at baseline (T1). All assessments were executed by a blinded researcher in the patients'

homes, at the same time of day in the "on" [26] phase, approximately 1 hour after medication intake. Figure 1 represents the RESCUE trial study design in which the T1-T4 measurements represent the time points on which the outcome measures FoG, FoF, and anxiety were assessed.

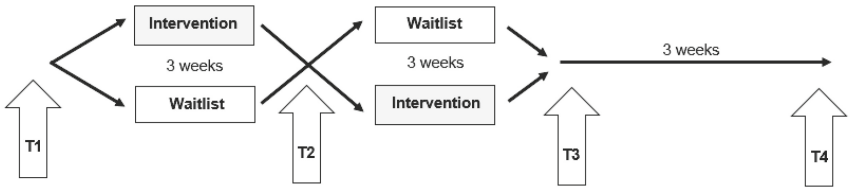

Figure 1. Timeline of the RESCUE trial with cross-over design. T1-T4 represent the moments on which outcome measures have been collected.

Outcome measures

The Freezing of Gait Questionnaire (FOGQ) is a validated questionnaire which assesses the FoG from a patient's perspective [27, 28]. The FOGQ consists of six questions which refer to the patient's experiences, related to FoG, in the previous week. Each question has a 5-point scale, where 0 represents an absence of symptoms and 4 represents the highest prevalence or severity of symptoms. Consequently, the total score on the FOGQ ranges from 0 to 24 points. The higher the score, the more pronounced the FoG.

FoF was assessed with the Falls Efficacy Scale (FES) [29]. The FES is a questionnaire to assess an individual's confidence and its self-efficacy to avoid a fall. The FES consists of 13 questions. Each question has an 11-point scale, where 0 represents an absence of confidence and 10 represents complete confidence during the mentioned activity. The inverse scale of the questionnaire was used, thus the higher the score the more FoF.

For measuring anxiety symptoms, we used the Hospital Anxiety and Depression Scale (HADS), a valid and responsive tool for measuring anxiety and depressive symptoms in PD over the past four weeks [13, 30]. The HADS is a self-report questionnaire that consists of seven anxiety and seven mood items. The total score in each subscale ranges from 0 (absence) to 21 (maximum). We used the scores of the anxiety (HADSA) and mood (HADSD) subscales separately. The reliability of the HADSA, for use in PD, is good with a Cronbach's alpha of 0.82 and an Intraclass Correlation Coefficient of 0.80 [30].

Statistical analyses

Linear mixed model analyses were used to assess the longitudinal associations between the outcome measures. Because repeated measurements, four time-points over 12 weeks, were nested within subjects, multilevel analyses is most appropiate [31]. Concerning missing values, multilevel analysis is quite good in handling missing data in the outcome variables because of this estimating method [32].

This longitudinal study consists of four repeated measurements of 153 patients, which means that the number of dummy variables would be large, compared to the total number of observations, and therefore it would be impossible to analyze the data in this way. In multilevel analysis the variance of the intercepts is estimated, not the separate intercepts for each patient. In this way, only one variance parameter (the 'random' intercept) is estimated. Equally, when it comes to the change of the outcome measures over the time points, the variance of the slopes is the one parameter that is estimated and further used in the analysis.

Separate linear mixed model analyses were used to analyse the following longitudinal univariable associations: 1) between FoG and FoF; 2) between FoG and anxiety, in which the first-mentioned variable (FoG) of the associations is dependent, and the latter the independent variable. Subsequently, the longitudinal multivariate association 3) between FoF and anxiety together as independent variables, and FoG as dependent variable, was analysed to investigate which variable is contributing the most to the association with FoG.

To investigate possible confounding factors, all associations were adjusted for the following groups of variables:

* Demographics; including gender [33-35], age [36] and body mass index [37-40].

** Disease characteristics; including UPDRS motor section 3 [41], disease duration [42], H&Y, HADSD [43], falls diary, the speed of the 10 meter walking test [44], standing balance (single leg stance test [45]), monitored physical activity (accelerometer), fatigue (multidimensional fatigue inventory (MFI)), cognitive executive function [46] (Mini Mental State Examination and Brixton Test Scaled score [47]).

*** Medication use; including Levodopa, dopamine agonist, catechol-O-methyl transferase inhibitor (Entacapone), selegiline and other (the type of medication that a patient used was registered), and adverse effects (using the UPDRS part IV B).

All analyses were adjusted for treatment allocation and performed with MLwiN (version 3.00). A two-tailed significance level of 0.05 was used.

Results

Table 1 shows the baseline characteristics of the 153 included PD patients. One patient dropped out 3 weeks after randomization because of a necessary change of drug treatment. Most patients had mild to moderate disease severity. At baseline, 41% of patients had at least weekly freezing episodes, defined by a score >1 on item 3 of the FOGQ and a quarter reported clinically relevant anxiety symptoms, considering the cut-off of 8 on the HADSA [48].

Table 2 shows the mean and standard deviations of the outcome measures over all four time points. For elaborate description of the intervention effects we refer to the study of Nieuwboer and colleagues [24]. Briefly, after receiving the intervention, only patients who experienced at least weekly freezing, reported a reduction in severity of FoG. In the total sample, greater confidence as measured with the FES and no significant changes in anxiety were reported.

Table 2. Time-variations in Freezing of Gait, Fear of Falling, and Anxiety outcome measures.

Outcome measure	Timepoint; Mean (sd)			
	T1	***T2***	***T3***	***T4***
FOGQ *[range: 0-24]*	8.7 (5.3)	8.2 (5.2)	7.5 (5.1)	8.3 (5.3)
FES *[range: 0-130]*	81.6 (27.9)	84.6 (27.7)	86.9 (27.0)	84.1 (28.6)
HADSA *[range: 0-21]*	6.9 (3.9)	6.5 (3.7)	6.4 (3.8)	6.7 (3.8)

Abbreviations: sd = standard deviation; FOGQ = Freezing of Gait Questionnaire; FES = Falls Efficacy Scale; HADSA = Hospital Anxiety and Depression Scale – Anxiety.

Figure 2 displays the crude analyses results (regression coefficients) of the univariate associations 1) between FoG and FoF, 2) between FoG and anxiety, and the multivariate association 3) between FoG (dependent) and FoF and anxiety (independent variables). All crude associations were positive and significant.

Table 1. Patients characteristics at baseline (N=153).

	Median (IQR)
Demographics	
Gender [a]	88 male/65 female
Age (years)	68 (11)
Body Mass Index	24.21(4.16)
Disease characteristics	
Disease duration (years)	8 (8)
Hoehn & Yahr during on	3 (1)
Hoehn & Yahr II/III/IV during on [a]	71/64/18
Unified Parkinson's Disease Rating Scale total score, during 'on' state	54 (17)
UPDRS I during on	3 (2)
UPDRS II during on	16 (8)
UPDRS III during on	32 (14)
Hospital Anxiety and Depression Scale - depression subscale	7 (5)
Brixton Test Raw score	21 (12)
Brixton Test Scaled score	4 (4)
Mini Mental State Examination	29 (3)
Multidimensional Fatigue Index	64 (25)
Static activity (% time)	90 (12)
Dynamic activity (% time)	10 (11)
Speed of 10-meter walking test (m/s)	0.85(0.29)
Single leg stance test left (sec)	7.64(17.3)
Single leg stance test right (sec)	8.68 (17.88)
Medication	
Levodopa (mg)	400 (350)
Dopamine agonist a	105
Selegeline [a]	22
Entacapone [a]	37
Medication other [a]	46
Adverse effects	
UPDRS IV (ON)	2 (4)

Abbreviations: IQR = Interquartile range, UPDRS = Unified Parkinson's Disease Rating Scale, [a] Expressed as number of patients.

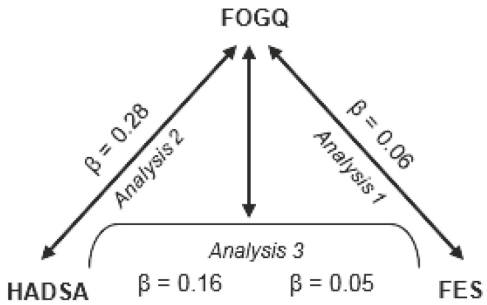

Figure 2. Crude analyses results of the univariate associations 1) between FoG and FoF, 2) between FoG and anxiety, and the multivariate association 3) between FoG (dependent) and FoF and anxiety (independent variables). Abbreviations: FOGQ = Freezing of Gait Questionnaire; FES = Falls Efficacy Scale; HADSA = Hospital Anxiety and Depression Scale; β = beta regression coefficient; FoG = Freezing of Gait; FoF = Fear of Falling.

The regression coefficient between FoG and FoF (analysis 1) showed the greatest change when adjusted for disease characteristics. The greatest change in regression coefficient in the association between FoG and anxiety (analysis 2) was seen after adjustments for medication and adverse effects. Table 3 shows the results of all crude and adjusted univariate associations.

When analysing FoF and anxiety together as independent variables (analysis 3, see table 4), the association between FoG and FoF remained as in the univariate analysis (analysis 1), while the association between FoG and anxiety weakened (as compared to analysis 2). In this multivariate association model, as in the separate univariate associations, the regression coefficient between FoF and FoG decreased the most after adjustment for disease characteristics. In addition, the regression coefficient between anxiety and FoG decreased the most after adjustment for medication and adverse effects, as was also seen in the univariate association.

Discussion

To our knowledge, this is the first study to investigate the longitudinal associations between FoG, FoF, and anxiety in a large cohort of PD patients. As expected, crude associations between FoG and FoF, and between FoG and anxiety were positive and significant. Adjustments for disease characteristics, medication and adverse effects showed the greatest decrease in the strength of these associations. When analysing

Table 3. Crude and adjusted regression coefficients for the following relationships: 1) between FoG and FoF, 2) between FoG and anxiety.

	β	95% CI	p-value	Change β compared to crude
1) FoG/FoF				
Crude	0.06	0.05 to 0.07	<0.001	
Adjusted group 1*	0.06	0.05 to 0.08	<0.001	0%
Adjusted group 2**	0.03	0.01 to 0.05	0.001	-50%
Adjusted group 3***	0.04	0.03 to 0.05	<0.001	-33,3%
2) FoG/anxiety				
Crude	0.28	0.17 to 0.38	<0.001	
Adjusted group 1*	0.21	0.10 to 0.32	0.001	-25%
Adjusted group 2**	0.18	0.08 to 0.29	0.002	-35,7%
Adjusted group 3***	0.10	0.001 to 0.19	0.048	-64,3%

*Abbreviations: FoG = Freezing of Gait, FoF = Fear of Falling, β = regression coefficient, CI = confidence interval. * Adjusted for demographics, **Adjusted for disease characteristics, ***Adjusted for medication and adverse effects.*

Table 4. Crude and adjusted regression coefficients for the relationship 3) between FoG (dependent) and FoF and anxiety (independent variables).

	Crude FoG			
	β	95% CI	p-value	
FoF	0.05	0,04 to 0.07	<0.0001	
Anxiety	0.16	0.06 to 0.26	0.003	
	Adjusted group 1*			Change in β compared to crude
FoF	0.06	0,04 to 0.07	<0.0001	+20%
Anxiety	0.11	0.01 to 0.22	0.0363	-31,3%
	Adjusted group 2**			
FoF	0.03	0,02 to 0.05	<0.0001	-40%
Anxiety	0.16	0.05 to 0.26	0.0034	0%
	Adjusted group 3***			
FoF	0.038	0,02 to 0.05	<0.0001	-24%
Anxiety	0.042	0.05 to 0.14	0.3816	-73,7%

*Abbreviations: FoG = Freezing of Gait, FoF = Fear of Falling, β = regression coefficient, CI = confidence interval. * Adjusted for demographics, **Adjusted for disease characteristics, ***Adjusted for medication and adverse effects.*

FoF and anxiety together as independent variables to investigate which variable is contributing the most to the association with FoG, the regression coefficient of the contribution of anxiety decreased.

In the small but evident contribution of FoF to FoG (analysis 1), the confounding effects of disease characteristics and medication and adverse effects may be explained by the fact that disease characteristics influence both FoG and FoF, and that FoG may occur in the 'on', 'transition' and 'off' state [8]. In their cross-sectional study comparing PD patients (n=58) with age-matched healthy controls, Adkin et al. [49] reported that FoF correlated positively with gait and balance instability in PD. Current FoG treatment proves to be insufficient, since 70% [8] of the fall incidents occur during a FoG episode. Clearly, FoF and FoG are highly related to one another, and it appears that the state ('on' and 'off') plays an important role in this association.

The positive association between FoG and anxiety (analysis 2) remained significant after adjusting for demographics; disease characteristics; medication and adverse effects. This finding, using a longitudinal design, is in line with the experimental study of Ehgoetz Martens et al. [3], who showed that anxiety directly resulted in FoG. Using a cross-sectional design, Lieberman [50] found a correlation between the presence of FoG, anxiety and panic scores in PD patients (n=109). In our PD cohort, a quarter of the patients reported clinically relevant anxiety symptoms, which rises to the assumption that even without high anxiety scores, the impact of anxiety on FoG is evident and might even cause episodes of FoG.

When analysing the multivariate association of FoF and anxiety with FoG (analysis 3), the contribution of anxiety diminished as the contribution of FoF remained the same in comparison with the univariate associations. Therefore, the univariate association between FoG and anxiety is largely explained by FoF. One might speculate about the direction of the associations, where the most logical direction resulting from our analyses would be from anxiety to FoF to FoG. As Rahman and colleagues [17] showed, anxiety is a predictor for avoidance behaviour in PD patients who experience FoF. FoF [11] and anxiety [51] both can lead to avoidance and restriction of activities and social life, and we speculate that this behavior will aggravate FoF and lead to even more physical decline. Further research is necessary to investigate the possible mediating effect of anxiety on the relationship between FoF and FoG.

We found that crude associations between FoG and FoF and between FoG and anxiety (analyses 1 & 2) remain significant after adjustment for demographics and disease characteristics. Adjusting the multivariate model (analysis 3) for

medication and its adverse effects renders the relationship between FoG and anxiety insignificant. FoG is easily exacerbated by multiple factors such as disease progression [42], cognitive dysfunctions such as attention [52], long-term use of medication, fluctuations and adverse effects [8]. Our results confirm that FoG should probably not be addressed with only drug treatment [53], since its adverse effects also play an important role. When adjusting the multivariate model for disease characteristics, the contribution of FoF to FoG diminishes (although remains significant). A low acitivity level has been described as a possible confounder in FoF and FoG [51]. FoF studies unrelated to PD show conflicting results, regarding the relationship between FoF and physical deterioration [65,66]. These studies in elderly without PD reported that FoF is related to physical inactivity and an increased risk of falling. In our PD cohort, low activity levels were also found (dynamic activity (% time) median = 10, IQR = 11).

With regard to the effect of medication and adverse effects on the reported associations between FoG, FoF, and anxiety, literature on response fluctuations is relevant. With disease progression and chronic exposure to levodopa, many patients develop a range of levodopa-induced motor and non-motor response fluctuations, including wearing-off. Patients with wearing-off symptoms report higher depression and anxiety scores in the 'off' state, as compared to the 'on' state [54]. In addition, panic attacks, which represent a high level of anxiety, are more frequent in the 'off' than in the 'on' state [55, 56]. Non-motor symptoms, such as anxiety, can fluctuate with pulsatile dopaminergic treatment. Also, non-motor fluctuations can vary unpredictably during the day [57]. The here reported effect of medication and its adverse effects in our FoG – anxiety association may be explained by the fact that higher anxiety and depression scores are related to complications of medication [51]. Medication and its adverse effects seem to influence both FoG and anxiety symptoms [58] and their association.

Psychological approaches, such as cognitive behavioral therapy, explicitly focus on anxiety symptoms, which are typically seen separate from the motor symptoms. However, due to the mutual interactions between FoG, FoF, and anxiety, and the impact of medication and its adverse effects, this artificial separation between psychological and somatic health care seems unnatural and may prevent optimal diagnostics and treatment. An integrated treatment with psychological and physiotherapeutic elements is necessary in order to address the interactions between motor and non-motor symptoms. For example, the body awareness (BEWARE) training [5] is designed to specifically address these PD related problems.

Study Limitations

Some limitations need to be acknowledged. Recall bias for the questionnaires is a limitation that must be considered. Also, the questionnaires contain different periods in time to which the questions apply, which might have altered the direct 'in the moment' symptom associations. For example, the FOGQ measures symptoms of freezing over the past week, the HADS measures anxiety symptoms over the past four weeks, which represents a longer period of time as compared to the FOGQ. Conclusions about cause-and-effect relationships can therefore not be made. Caution must be taken in generalizing the current findings to the general PD population, since this cohort had specific inclusion- and exclusion criteria.

Starkstein and colleagues [59] indicate that increased depressive symptoms and anxiety often co-exists. In our study, PD patients were excluded when having a HADSD ≥ 8 which may have resulted in a study sample with relatively mild anxiety and mood disturbances. However, the results are robust within this large sample of PD patients and it is to be expected that an even stronger mutual interaction between FoG-FoF-anxiety could be found with higher levels of depressive and anxiety symptoms.

Conclusion

Our findings, based on a longitudinal design, show positive associations between FoG, FoF, and anxiety, suggesting that these symptoms interact and may aggravate each other. These reported interactions between motor and non-motor problems in PD underline the importance of an integrated interdisciplinary approach in diagnostics and treatment in these patients.

Future perspectives

The findings of our study contribute to increased awareness of the reciprocal interactions between motor and non-motor symptoms. This insight should lead to more multidisciplinairy oriented approaches in the diagnostics and treatment, such as the BEWARE training [5], aimed to learn how to deal with the motor and non-motor aspects of symptom fluctuations in PD.

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6

The effects of cognitive behavioral and mindfulness-based therapies on psychological distress in patients with Multiple Sclerosis, Parkinson's disease and Huntington's disease: two meta-analyses

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Abstract

Objective: Psychological distress has a high impact on quality of life in patients with multiple sclerosis (MS), Parkinson's disease (PD), and Huntington's disease (HD). Studies have shown that cognitive behavioral therapy (CBT) and mindfulness-based therapies (MBTs) are successful in reducing psychological distress in patients with anxiety, depressive, and chronic somatic disorders. We aimed to investigate the effectiveness of these therapies in MS, PD, and HD patients.

Methods: We performed a comprehensive literature search in PubMed, PsycINFO, Embase and the Cochrane Central Register of Controlled Trials up to March 2018. Randomized controlled trials (RCTs) investigating a CBT or MBT and reporting psychological outcome measures were included. Two separate meta-analyses were performed; one on studies comparing psychological therapy with a treatment as usual or waitlist condition and one on studies with active treatment control conditions.

Results: The first meta-analysis (N = 12 studies, 8 in MS and 4 in PD populations) showed a significant effect size of g = 0.51 in reducing psychological distress. The second meta-analysis (N = 7 studies, in MS populations) showed a mean effect size of g = 0.36. No RCTs were found in HD populations. The overall quality of the included studies was low and considerable heterogeneity was found. No evidence was found for publication bias.

Conclusion: CBT and MBTs have a small to moderate effect on reducing psychological distress in patients with PD and MS. However, more research with better methodological quality and larger study samples is warranted, especially in HD patient populations.

Introduction

Progressive neurological disorders, such as Multiple Sclerosis (MS), Parkinson's disease (PD) and Huntington's disease (HD), are often accompanied by psychological distress [1-3]. Psychological distress can be defined as negative mental health states and includes anxiety and depressive symptoms. Psychological distress has a higher impact on the quality of life of both the patients and their caregivers as compared to the physical symptoms that accompany the diseases [4, 5].

The resemblance between MS, PD and HD includes the progressive nature of the disease, uncertainty on disease course, and incurability (only symptom reduction is possible), which contribute to psychological distress. In addition to these factors, psychological distress can arise from physical symptoms such as spasms, rigidity, and autonomic dysregulation, resulting in a vicious circle where physical and psychological symptoms reinforce one another. On the neurobiological level, frontostriatal circuits are affected by the disease, causing disruptions in cognition, affect, motivation, behavior, and stress regulation [6, 7]. Because of these similarities, it is likely that these three patient populations can equally benefit from psychological treatments. This hypothesis is supported by the finding that a standardized psychosocial self-management program proved to be effective in a variety of chronic diseases, including MS, PD, and HD [8].

A considerable number of studies has investigated potential effective treatments for psychological distress reduction. These treatments are cognitive behavioral and mindfulness-based. In an extensive review and meta-analysis, Hofmann and colleagues [9], showed that cognitive behavioral therapy (CBT) is an effective treatment for psychological distress and, more specifically, anxiety symptoms in patients with psychiatric and medical conditions. Besides classical CBT, problem solving and self-management therapies are also considered CBT-based since these interventions are based on the same principles. In PD patients, CBT also showed positive effects in treating anxiety and depressive symptoms [10-12]. In MS, Dennison and colleagues [13] concluded that CBT is effective in improving the management of somatic symptoms and psychological distress. According to Novak and Tabrizi [14], depression and anxiety are usually treated with medication in HD patients, but CBT is also effective in well-selected patients that experience mild symptoms and who have insight in their psychological problems. However, no controlled studies have been performed in this patient group.

Besides CBT, mindfulness-based treatments (MBTs) receive increasing attention in clinical practice. Mindfulness involves 'paying attention in a particular way: on purpose, in the present moment, and non-judgmentally' [15]. MBTs include mindfulness-based stress reduction, mindfulness-based cognitive therapy, meditation, and acceptance and commitment therapy. MBTs have been proven to be effective in reducing anxiety and depressive symptoms in patients with anxiety and depressive disorders [16], and patients with chronic pain [17]. Also, small to moderate effect sizes in improving mental health were found in populations with different chronic somatic diseases [18, 19], and medium effect sizes were found in MBTs for MS patients [20].

To reduce psychological distress in patients with progressive neurological disorders, CBTs and MBTs might thus be of potential benefit. Since these interventions are considered treatment options, it is warranted to investigate their effectiveness. In order to establish the efficacy of CBTs and MBTs on reducing psychological distress in PD, HD, and MS patients, we performed a meta-analysis on randomized controlled trials.

Method

Selection of studies

A comprehensive literature search was conducted in PubMed, PsycINFO, the Cochrane library and EMBASE through March 2018. In addition, *ClinicalTrials.gov* was searched for completed but unpublished studies. The following keywords were used: "Parkinson", "Huntington", "Multiple Sclerosis", "psychological distress", "stress reduction", "distress", "depressive symptoms", "anxiety symptoms" (see the supplementary material for the complete search string). Besides the database searches, recent meta-analyses [21-23] were read to find additional studies. Two researchers (IG, SR) independently selected the studies for inclusion and when they disagreed a consensus was made.

Inclusion criteria for the meta-analyses were:

- Patients: a study population of MS, PD, or HD patients.
- Intervention: the examination of a CBT- or MBT-based intervention.
- Comparison: the intervention was compared with a waitlist or treatment-as-usual (TAU) condition, or with another active form of therapy. Only randomized controlled trials (RCTs) were included in this meta-analysis.

- Outcome: availability of questionnaires that measure anxiety and/or depressive symptoms, or general mental health. These data should allow the calculation of standardized mean differences (post-treatment means, standard deviations, and number of participants; or other statistics that allowed to calculate effect sizes).

The study abstract or manuscript should be available in English or Dutch.

Data extraction

All decisions on the inclusion of outcome measures for psychological distress, including depressive and anxiety symptoms, or/and general mental health outcome measures, were based on consensus between two researchers (IG, SR). Outcome measures of psychological distress were extracted by these two researchers, independently. Post-treatment measurements were collected to examine the immediate effect of the interventions. When data were not available, the study researchers were contacted. In addition, two independent researchers (RB, MH) rated the type of interventions (CBT or MBT) investigated in the studies, based on the treatment components described in the manuscript.

Quality assessment

The methodological quality of the included studies was assessed with seven criteria of the risk of bias assessment tool, developed by Cochrane [24] to assess sources of bias in RCTs:

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and researchers (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other bias

When questionable or unclear risk of bias was found, this was considered a risk of bias. Again, quality assessment was performed by two independent researchers (IG, SR).

Meta-analyses

The Hedges' *g* effect sizes were calculated for each study and pooled with Comprehensive Meta-analysis (CMA; version 3 for Windows). Post-treatment means

and corresponding standard deviations measures were used to calculate Hedges' *g*. Means and standard deviations from anxiety, depression, and general mental health outcome measures within each study were pooled within the CMA program so that one 'psychological distress' measure for each study was included in the meta-analyses. Two separate main meta-analyses were conducted: the first to investigate psychological interventions that were compared with waitlist or TAU conditions, the second to investigate psychological interventions that were compared with other active interventions (such as supportive listening, relaxation, and psycho-education).

Within the first main meta-analysis, besides the combined psychological distress measure, the individual effect sizes on anxiety, depression, and general mental health outcomes were investigated using separate smaller meta-analyses. Subgroup analyses were conducted for disease type, control condition, and high vs low risk of bias. In addition, the relationship between risk of bias and effect size was investigated with a regression analysis. Within the second main meta-analysis, the different types of interventions of interest (CBTs and MBTs) were investigated by performing two separate meta-analyses. There were too few studies to perform further subgroup analyses.

As considerable heterogeneity was expected, all analyses were conducted using the random effects model. The I^2 statistic was calculated as an indicator of heterogeneity. We calculated the 95% confidence intervals (95% CI) around I^2 [25] using the non-central chi-squared based approach within the heterogi module for Stata [26]. When the I^2 estimate reached 40%, this was classified as considerable heterogeneity [27].

Subgroup analyses were conducted according to the mixed-effects model [28], and the meta-regression analysis was conducted according to the procedures developed by Borenstein et al. [28].

Publication bias was examined with Duval and Tweedie's trim and fill procedure which estimates how many studies are missing in the meta-analyses and then imputes these [29], as well as Egger's test for the asymmetry of the funnel plot.

The protocol of this meta-analysis was not pre-registered.

Results

Selected studies

After removing duplicate studies, 156 records were found. After inspection of the titles and abstracts, 24 full-text articles were retrieved. In addition, four studies were included from past meta-analyses, resulting in 28 full-text articles that were read. Figure 1 presents the flowchart of the inclusion process with reasons for exclusion, following the PRISMA statement [30]. Eventually, 19 studies were included, of which 12 were included in the first meta-analysis, and seven in the second meta-analysis.

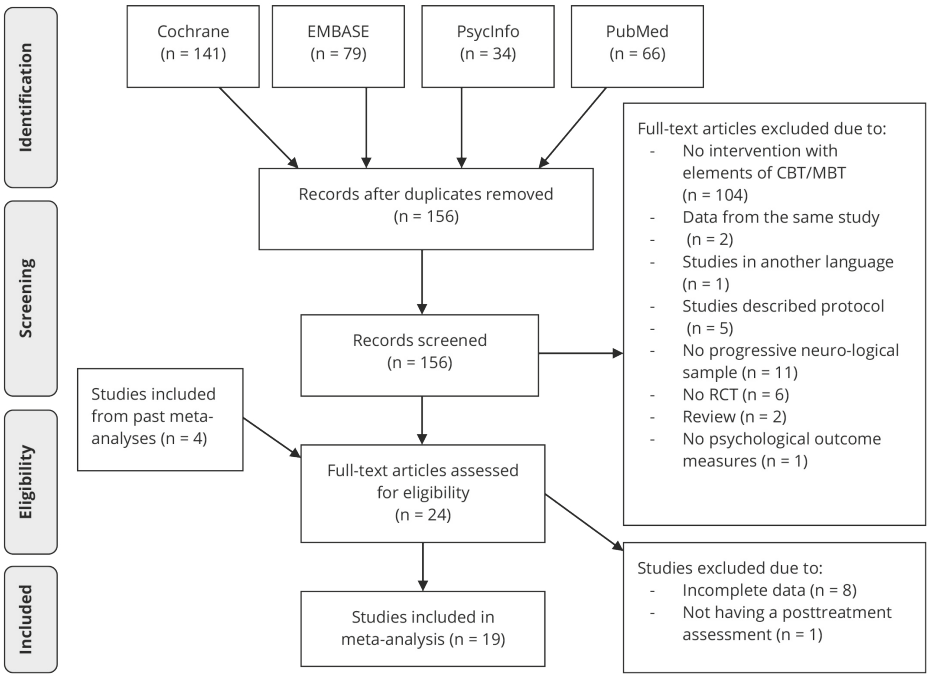

Figure 1. PRISMA flow chart of selection and inclusion process. CBT = Cognitive Behavioral Therapy, MBT = Mindfulness Based Therapy; RCT = randomized controlled trial.

Characteristics of included studies

Table 1 shows the characteristics of the included studies, displayed separately for the two main meta-analyses. Within the first analysis, eight studies included MS patients [31-38], four studies included PD patients [39-42], and no RCTs were found investigating HD populations. Nine studies examined a CBT-based intervention [31, 33-37, 39, 41, 42] and three studies investigated an MBT [32, 38, 40].

Within the second analysis, only MS patients were investigated in the included studies. Regarding the treatments of interest, four studies investigated a CBT-based treatment [43-46] and three examined an MBT [47-49].

Overall, the quality of the included RCTs was low, based on the scores on the risk of bias assessment tool. Blinding of participants/researchers was impossible due to the nature of studies on psychotherapeutic interventions, and was therefore always considered as risk of bias. As allocation concealment was often not well reported, two studies had a risk of detection bias [41, 47]. The study by Okai and colleagues [41] also showed an attrition bias, as did the study by Calleo and colleagues [39]. In the first analysis, four studies showed good quality [31, 33, 38, 42], as shown by a total risk of bias of 1 (only risk of performance bias). In the second analysis, only the study by Carletto and colleagues had good quality (score of 1 on the risk of bias assessment tool: only blinding of participants was not achieved) [49].

Treatment Effects

Meta-analysis 1: psychological therapy versus TAU or waitlist condition
Figure 2 displays the forest plot of the standardized effect sizes of psychological therapies on psychological distress in PD and MS patients, compared with a waitlist or TAU condition. The mean effect size (*g*) was 0.51 (95% CI = 0.22 — 0.80) with a heterogeneity estimate (I^2) of 66 (95% CI = 27 — 80).

As a post-hoc analysis, the studies of Okai et al. [41], Ghielen et al. [40], and Kiropoulos et al. [35] were excluded in a separate meta-analysis. These studies were considered outliers since the effect sizes with their 95% confidence intervals were outside the 95% confidence interval of the pooled main effect size. The effect size decreased to *g* = 0.31 (95% CI = 0.13 — 0.48) and heterogeneity decreased to I^2 = 0 (95% CI = 0 — 56) when these three studies were removed (see table 2).

To investigate the treatment effects on the different types of outcome measure separately, three meta-analyses were conducted on anxiety, depression, and general psychological distress outcome measures. The treatment effect on general mental health outcomes was highest (*g* = 0.79, 95% CI = 0.32 — 1.25 with I^2 = 66, 95% CI = 0 – 85), followed by the effect on anxiety symptoms (*g* = 0.36, 95% CI = 0.03 — 0.66 with I^2 = 59, 95% CI = 0 — 79), and depressive symptoms (*g* = 0.33, 95% CI = 0.05 — 0.62 with I^2 = 60, 95% CI = 0 — 78) (see table 2).

Table 1. Study characteristics.

Study	Medical condition	Comorbidity	Primary outcome	N intervention	Intervention	N control	Control	Outcomes in analysis	Risk of bias (0-7)*
Meta-analysis 1									
Boeschoten et al. (2016) [31]	MS	Moderate/severe depressive symptoms	BDI-II	85	IPST	86	WL	BDI-II HADS-A BAI	0-0-1-0-0-0-0 (1)
Bogosian et al. (2015) [32]	MS	Psychological distress	GHQ	19	Mindfulness	21	WL	GHQ HADS-A HADS-D	0-?-1-0-0-0-0 (2)
Fischer et al. (2013) [33]	MS	Depressive symptoms	BDI-II	45	CBT	45	WL	BDI-II	0-0-1-0-0-0-0 (1)
Forman et al. (2010) [34]	MS	Anxiety and/or depressive symptoms	HADS & GHQ	20	CBT	20	WL	HADS-A HADS-D	0-?-1-0-0-0-0 (2)
Kiropoulos et al. (2016) [35]	MS	Depressive symptoms	BDI-II	15	CBT	15	TAU	BDI-II STAI	0-0-1-1-0-0-0 (2)
Lincoln et al. (2011) [36]	MS	Anxiety and/or depressive symptoms	GHQ	72	CBT	79	WL	BDI GHQ HADS-A HADS-D	0-?-1-0-0-0-0 (2)
Mohr et al. (2000) [37]	MS	Moderate depressive symptoms	POMS-DDS	16	CBT	16	TAU	POMS-DDS	?-?-1-?-0-1-0 (5)
Simpson et al. (2017) [38]	MS	No inclusion criteria	PSS	25	MBSR	25	WL	PSS	0-0-1-0-0-0-0 (1)
Calleo et al. (2015) [39]	PD	Anxiety and/or depressive symptoms	Feasibility & satisfaction	10	CBT	6	TAU	HADS-A HADS-D	0-0-1-0-1-?-0 (3)

MS = Multiple Sclerosis, PD = Parkinson's Disease, CBT = Cognitive Behavioral Therapy, MBSR = Mindfulness Based Stress Reduction, ACT = Acceptance & Commitment Therapy, IPST = Internet-based Problem Solving Therapy, BAM = Body-Affective Mindfulness, PT = Physical Therapy, WL = Wait-List, PE = Psycho-Education, SL = Supportive Listening, TAU = Treatment As Usual, HADS = Hospital Anxiety and Depression Scale (A = anxiety, D = depression), BDI = Beck Depression Inventory, PSS = Perceived Stress Scale, GHQ = General Health Questionnaire, PHQ = Patient Health Questionnaire, NPI = NeuroPsychiatric Inventory, POMS = Profile Of Mood Scale, GSES = General Self-Efficacy Scale, BAI = Beck Anxiety Inventory, HRSD = Hamilton Rating Scale for Depression.

Table 1. Study characteristics. (continued)

Study	Medical condition	Comorbidity	Primary outcome	N intervention	Intervention	N control	Control	Outcomes in analysis	Risk of bias (0-7)*
Ghielen et al. (2016) [40]	PD	Anxiety symptoms	GSES	19	ACT+PT	19	TAU (PT)	BAI BDI	0-0-1-0-0-0-1 (2)
Okai et al. (2013) [41]	PD	Impulse control disorder(s)	NPI	28	CBT	17	WL	GHQ	?-0-1-1-1-0-0 (3)
Troeung et al. (2014) [42]	PD	Anxiety and/or depressive symptoms	DASS	11	CBT	7	WL	DASS-A DASS-D DASS-S	0-0-1-0-0-0-0 (1)
Meta-analysis 2									
Ehde et al. (2015) [43]	MS	Fatigue, pain, or depressive symptoms	PHQ	75	Self-management	88	PE	PHQ	0-0-1-0-0-0-1 (2)
Mohr et al. (2001) [44]	MS	Major depressive disorder	HRSD & BDI	20	CBT	22	Supportive expression	BDI HRSD	1-?-1-?-0-0-? (5)
Mohr et al. (2005) [45]	MS	Moderate depressive symptoms	HRSD & BDI-II	62	CBT	65	Supportive expression	BDI-II HRSD	1-?-1-0-0-0-0 (3)
Moss-Morris et al. (2013) [46]	MS	Psychological distress	GHQ	48	CBT	46	SL	GHQ	0-0-1-0-0-?-0 (2)
Nordin et al. (2012) [47]	MS	Anxiety and/or depressive symptoms	HADS	11	ACT	10	Relaxation	BDI HADS-A HADS-D	0-?-1-1-0-0-0 (3)
Oreja-Guevera et al. (2015) [48]	MS	Unknown	HADS	21	MBSR	20	PE	HADS-A	Not assessable
Carletto et al. (2017) [49]	MS	Depressive symptoms		43	BAM	45	PE	BDI-II BAI PSS	0-0-1-0-0-0-0 (1)

**Risk of bias is derived after assigning a zero (low risk of bias (0)) or one (unclear (?) or high risk of bias (1)) to each one of the following quality criteria: allocation sequence, allocation concealment, blinding of participants and personnel, blinding of assessors, incomplete outcome data, selective reporting, and other sources of bias, and a sum score.*

Table 2. Effect sizes and heterogeneity measures for CBTs and MBTs in improving psychological distress in PD and MS patients, including subgroup analyses.

	N (studies)	Hedges'g	95% CI	I^2	95% CI	p-value	NNT*
Meta-analysis 1							
All	12	0.51	0.22 – 0.80	66	27-80	<0.001	3.55
Excluding outliers[@]	8	0.31	0.13 – 0.48	0	0-56	0.008	5.75
Outcome							
Depression	10	0.33	0.05 – 0.62	60	0-78	0.042	5.43
Anxiety	8	0.36	0.03 – 0.68	59	0-79	0.038	5.00
Psychological distress	5	0.79	0.32 – 1.25	66	0-85	0.015	2.36
Subgroup analyses							
Disease type							
MS	8	0.54	0.26 – 0.82	45	0-72	0.003	3.36
PD	4	0.37	-0.55 – 1.29	80	16-91		4.85
Control condition							
Waitlist	7	0.39	0.18 – 0.60	26	0-68	0.006	4.59
TAU	5	0.67	-0.16 – 1.49	82	49-91		2.75
Risk of Bias [#]							
High	8	0.57	0.14 – 0.99	71	22-84	0.003	3.18
Low	4	0.42	0.02 – 0.81	61	0-85		4.27
Meta-analysis 2							
All	7	0.36	0.13 – 0.58	40	0-74	0.002	5.00
Treatment type							
CBTs	4	0.45	0.26 – 0.64	0	0-73	0.004	3.55
MBTs	3	0.06	-0.56 – 0.68	68	0-89	0.72	29.41

*MS = Multiple Sclerosis; PD = Parkinson's Disease; CBTs = Cognitive Behavioral Therapies; MBTs = Mindfulness Based Therapies; NNT = Number Needed to Treat; TAU = treatment as usual. *according to Kraemer & Kupfer [50].[@] outliers include Okai et al. [41], Kiropoulos et al. [35], Ghielen et al. [40].[#] low risk of bias include studies scoring 1 according to the risk of bias assessment tool, developed by Cochrane [24], a score > 1 is considered high risk of bias.*

In addition, subgroup analyses were conducted (table 2) to investigate differences in effect size for disease type, control condition, and risk of bias (high vs low). Significantly larger effect sizes were found in MS patient populations, TAU control condition, and studies with a high risk of bias.

Meta-regression analyses on risk of bias (β = 0.08, 95% CI = -0.18 – 0.33, p >0.05) did not show a significant relationship with effect size.

Meta-analysis 2: psychological therapy versus active control condition
Figure 3 shows the forest plot of the standardized effect sizes of psychological therapies on psychological distress in MS patients, compared with an active control condition. The mean effect size (*g*) was 0.36 (95% CI = 0.13 — 0.58) with a heterogeneity estimate (I^2) of 40 (95% CI = 0 — 74).

To investigate the treatment effects for the types of investigated intervention, two separate meta-analyses were conducted on CBT-based treatments and MBTs. The treatment effect for CBT-based treatments was highest (*g* = 0.45, 95% CI = 0.26 — 0.64 with I^2 = 0, 95% CI = 0 — 73), followed by a small effect for MBTs (*g* = 0.06, 95% CI = -0.56 — 0.68 with I^2 = 68, 95% CI = 0-89) (see table 2).

Publication bias

No evidence for publication bias was found in both meta-analyses. Inspection of the funnel plots did not indicate significant publication bias (figures 4 & 5). Duval & Tweedie's trim-and-fill procedure resulted in the imputation of four studies in the first meta-analysis, and no imputations in the second meta-analysis, according to a random model. Egger's regression intercept indicated no significant publication bias (p > 0.05 in both analyses).

Discussion

In this study, we investigated the effectiveness of CBT and MBT on psychological distress in patients with PD and MS by conducting two main meta-analyses of randomized controlled trials. There were no RCTs found studying these therapies in HD populations. Nineteen studies were included in the analyses, of which twelve compared the treatment of interest with a TAU or waitlist condition (meta-analysis 1), and seven studies compared the treatment of interest with an active control

Study name	Disease	Therapy	Control	Statistics for each study				Hedges' g and 95% CI
				Hedges' g	Lower limit	Upper limit	p-value	
Boeschoten et al. (2016) [31]	MS	IPST	WL	0.11	-0.21	0.42	0.51	
Bogosian et al. (2015) [32]	MS	Mindfuln	WL	0.55	-0.10	1.20	0.10	
Fischer et al. (2013) [33]	MS	CBT	WL	0.32	-0.09	0.74	0.12	
Forman et al. (2010) [34]	MS	CBT	WL	0.41	-0.22	1.04	0.20	
Kiropoulos et al. (2016) [35]	MS	CBT	TAU	1.64	0.83	2.46	<0.001	
Lincoln et al. (2011) [36]	MS	CBT	WL	0.38	0.04	0.73	0.03	
Mohr et al. (2000) [37]	MS	CBT	TAU	0.57	-0.12	1.26	0.11	
Simpson et al. (2017) [38]	MS	MBSR	WL	1.04	0.46	1.62	<0.001	
Calleo et al. (2015) [39]	PD	CBT	TAU	0.11	-1.01	1.24	0.84	
Ghielen et al. (2016) [40]	PD	ACT+PT	TAU	-0.45	-1.08	0.18	0.16	
Okai et al. (2013) [41]	PD	CBT	WL	1.44	0.71	2.17	<0.001	
Troeung et al. (2014) [42]	PD	CBT	WL	0.36	-0.56	1.27	0.46	
				0.51	***0.22***	***0.80***	***0.001***	

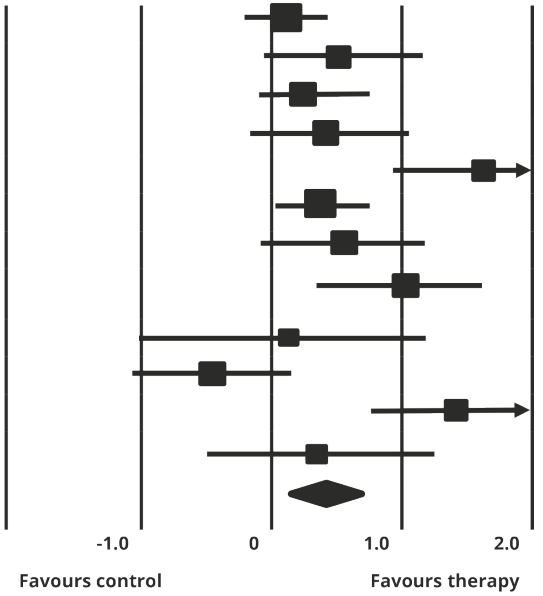

Figure 2. Forest plot of studies comparing CBTs and MBTs with TAU or WL conditions (meta-analysis 1). MS = Multiple Sclerosis; PD = Parkinson's disease; IPST = Internet-based Problem Solving Therapy; Mindfuln = Mindfulness; CBT = Cognitive Behavioral Therapy; MBSR = Mindfulness Based Stress Reduction; ACT = Acceptance & Commitment Therapy; PT = Physical Therapy; TAU = treatment as usual; WL = waitlist.

Study name	Disease	Therapy	Control	Statistics for each study				Hedges' g and 95% CI
				Hedges' g	Lower limit	Upper limit	p-value	
Ehde et al. (2015) [43]	MS	Self-management	PE	0.35	0.04	0.66	0.03	
Mohr et al. (2001) [44]	MS	CBT	Supportive expression	0.51	-0.10	1.11	0.10	
Mohr et al. (2005) [45]	MS	MBSR	PE	0.39	0.03	0.74	0.03	
Moss-Morris et al. (2013) [46]	MS	CBT	SL	0.69	0.27	1.12	0.001	
Nordin et al. (2012) [47]	MS	ACT	Relaxation	-0.10	-0.93	0.73	0.81	
Oreja-Guevera et al. (2015) [48]	MS	MBSR	PE	-0.37	-0.98	0.23	0.23	
Carletto et al. (2017) [49]	MS	BAM	SL	0.53	0.11	0.96	0.01	
				0.36	***0.13***	***0.58***	***0.002***	

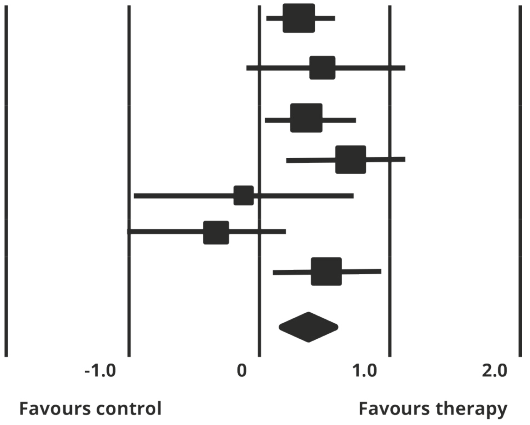

Figure 3. Forest plot of studies comparing CBTs and MBTs with active control conditions (meta-analysis 2). MS = Multiple Sclerosis; CBT = Cognitive Behavioral Therapy; MBSR = Mindfulness Based Stress Reduction; ACT = Acceptance & Commitment Therapy; PE = Psycho-Education; SL = Supportive Listening.

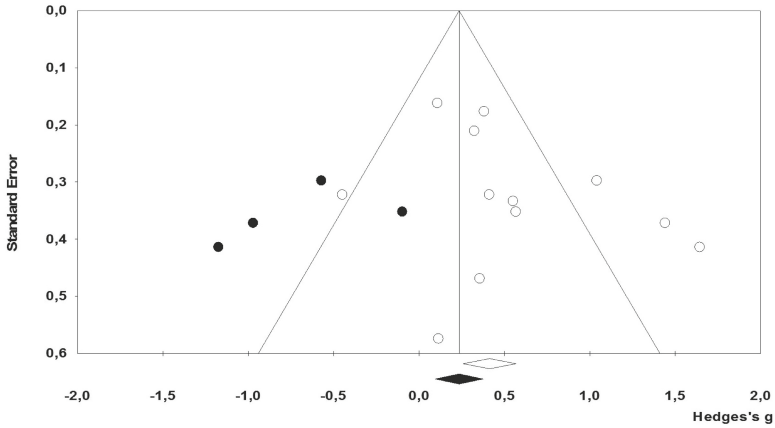

Figure 4. Funnel plot of meta-analysis 1: psychological intervention versus TAU or WL conditions. TAU = treatment as usual; WL = waitlist. The imputed studies are shown in black.

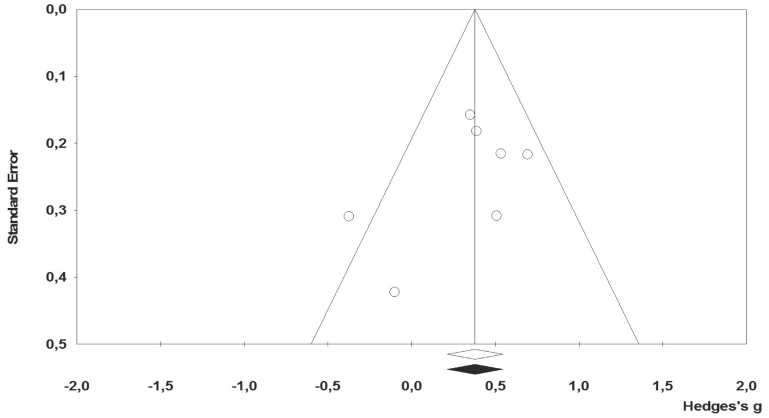

Figure 5. Funnel plot of meta-analysis 2: psychological intervention versus active control conditions.

condition (meta-analysis 2). A moderate effect size (g = 0.51) was found in the first meta-analysis, and a small effect size (g = 0.36) was found in the second meta-analysis. In both meta-analyses there was considerable heterogeneity, which was probably due to the variability in hours of treatment (range: 5-16 hours), different delivery forms (for example by telephone or face-to-face), differences in comorbidity in the included subjects over all included studies, and specific elements that varied between the interventions (such as psycho education in the study of Okai et al [41]). The heterogeneity decreased when 1) outliers were removed; 2) depression and anxiety outcomes were analyzed separately; 3) only looking at MS patient samples; 4) studies with waitlist control conditions were analyzed; and 5) studies with a low

risk of bias were analyzed. In these post-hoc analyses, the effect sizes decreased to small (g = 0.31, g = 0.33, g = 0.36, g = 0.39, g = 0.42, respectively). No evidence was found for publication bias.

The small to moderate main effect sizes suggest that CBT and MBT are beneficial in reducing psychological distress, but only to a certain extent. Biological approaches, e.g. pharmacotherapy, showed a reduction of depressive symptoms in MS patients with an effect size of 0.63 (standardized mean difference) [22]. According to the review and meta-analysis by Fiest et al. [22], current research is insufficient to determine the effectiveness of pharmacotherapy for anxiety in MS as no controlled studies were found. In PD, the meta-analysis of Bomasang and colleagues [51] on antidepressant medication showed an effect size of 0.54 in reducing depressive symptoms. The effect of pharmacotherapy on reducing symptoms of anxiety in PD patients has insufficiently been studied. Although the effect sizes of pharmacotherapy on depressive symptoms appear to be larger than those of psychological treatment, regarding anxiety and global mental health the effect is not yet investigated properly. One can imagine that pharmacological interventions show larger effect sizes compared to psychotherapeutic interventions, since the latter requires cognitive abilities to learn and apply the methods that are taught. Although patients with dementia were excluded in most studies, it is possible that these populations have reduced cognitive abilities as a result of the neurodegenerative process, and are therefore unable to optimally benefit from CBT and MBT. It is also argued that a combination of psychotherapy and pharmacotherapy might be most beneficial, at least for outpatients with chronic forms of depression [52, 53] and panic disorder [53]. In adults with an anxiety or depressive disorder without neurological comorbidity, a meta-analysis of Cuijpers and colleagues [54] showed that CBT is probably effective. Although effect sizes were larger (around g = 0.80) compared to our results, the quality of the included studies was low and publication bias was present. Large effect sizes were also found for MBTs in the treatment of anxiety and depressive symptoms in participants without neurological comorbidity [55]. Here, no publication bias was present but study quality was again unsatisfactory. CBT and MBT appear to be more effective in patients without compared to patients with neurodegenerative disorders. However, the methodological quality is insufficient to draw definite conclusions.

MS patients seem to benefit more from CBT and MBT than PD patients as is represented by the significant subgroup difference in effect size regarding disease type. However, considerable heterogeneity was present in both subgroups and all therapies described here were adapted to the respective study sample. The MS

population is best represented in these meta-analyses, including fifteen RCTs of which eight were included in the first meta-analysis. The second meta-analysis included only studies in MS populations. Overall, the mean age of MS patient groups was lower compared to the PD patient groups. One can imagine that having a progressive neurological disorder in an earlier or later phase of life results in different psychosocial issues and cognitive abilities to benefit from therapy.

A considerably large effect size was found in the pilot study of Okai and colleagues [41]. In this study, all PD patients additionally suffered from impulse control disorders. When the treatment components were critically investigated, it was notable that this was the only CBT-based intervention that included executive dysfunction education. PD patients often show an impairment in executive functioning in an early stage of the disease [56, 57]. Since this study showed a great improvement in psychological distress, this might indicate that executive dysfunction plays an important role in regulating negative emotions and cognitions, at least in PD patients with impulse control disorders. This, however, needs confirmation in future research.

The pilot study by Kiropoulos et al. [35] also showed a large effect size (g = 1.64). This study included newly diagnosed MS patients (< 5 years since diagnosis) and the age of these patients was lower compared to other studies that investigated MS populations. These patients might be less severely affected compared to other study populations. Comparisons, however, could not be made since studies reported different measures of disease severity. No differences were found concerning treatment components when compared with other CBT-based interventions in MS.

Of great importance is the focus of the treatment types and control conditions. The studies by Ghielen et al. [40], Oreja-Guevera et al. [48], and Nordin et al. [47] investigated MBTs. These three studies showed (non-significant) negative effect sizes of g = -0.45, g = -0.37, and g = -0.10, respectively, favoring the control condition in reducing psychological distress symptoms. These studies all included an active form of control condition: physical therapy (TAU), psycho education, and relaxation, which might have diminished the positive effect. Besides this, the focus of ACT is not on symptom reduction but on coping with the disease despite of the symptoms that are present. This is achieved by improving awareness of ones bodily sensations, thoughts and feelings. As one can imagine, when one is more aware of his/her symptoms, these will also be more often reported, resulting in a higher score on questionnaires.

This leads us into the discussion concerning the suitability of questionnaires to measure treatment effects. Since MBTs are focused on awareness and acceptance, and not aim to reduce symptoms, questionnaires that measure the prevalence or severity of symptoms are less appropriate. The studies by Bogosian et al. [32] and Simpson et al. [38], however, investigated mindfulness interventions and showed effect sizes of $g = 0.55$ and $g = 1.04$, respectively, in improving general mental health. In addition, when overall psychological distress was measured with general mental health questionnaires, a high effect size of $g = 0.79$, although with considerable heterogeneity, was found. The focus of an intervention, type of control condition, and the outcome measures used seem to be of importance in evaluating the effectiveness, and therefore need to be carefully considered when conducting an RCT.

Overall, the included studies had low quality, only three out of seventeen studies reached good quality according to the risk of bias tool. The findings need to be carefully interpreted since risk of bias is present in most of the studies and might have influenced the treatment effects. Each study suffers from different types of bias, except for the performance bias which is always a risk due to the nature of these intervention studies.

Limitations and implications

First, the effect size is solely based on studies in patients with PD and MS, since there were no RCTs found in HD that investigated the effect of psychological interventions on psychological distress. Second, MS patients might be overrepresented in the meta-analysis since fifteen out of nineteen RCTs investigated MS populations, resulting in the effect size being driven mostly by MS populations, especially in the second meta-analysis in which only MS populations were included. Heterogeneity estimates were above 40% in most analyses, reflecting high heterogeneity within the meta-analyses, and most studies included small sample sizes, which resulted in low power. Finally, the overall quality of the studies was low and the quality of one study could not be assessed.

It is therefore recommended to study psychological interventions in more detail and in larger patient samples in study designs with higher methodological quality. Especially in HD more research is needed, since no RCTs on the effects of psychological treatment were found in our literature search. It might also be interesting to investigate the addition of psychopharmacological therapies, besides

psychotherapy. Besides a primary focus on reducing psychological distress, we recommend to investigate the effect on coping with the disease, quality of life, valued living, or self-efficacy, especially in RCTs studying the effect of MBTs. Since progression of the disease is inevitable, it is therefore important to learn how to cope with the disease instead of focusing on symptom reduction only. Furthermore, caution is warranted in the choice of outcome measures and the type of control conditions as comparators, since these decisions greatly influence the study outcome. Lastly, it might be interesting to include executive dysfunction education in interventions for PD patients with impulse control disorders.

Conclusion

Despite the abovementioned limitations, we conclude that psychological interventions have a small to moderate effect on reducing psychological distress in patients with PD and MS. However, more research is warranted, especially in HD and PD patient samples. These studies need to have better methodological quality (e.g. lower risk of bias) and study samples should be larger to achieve a sufficient power.

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7

BEWARE: Body awareness training in the treatment of wearing-off related anxiety in patients with Parkinson's disease: study protocol for a single-blinded randomized controlled trial

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Abstract

Background: The wearing-off phenomenon in Parkinson's disease (PD) patients is a complication of prolonged levodopa usage. During this phenomenon, motor symptoms such as rigidity and freezing, re-emerge. This is often accompanied by non-motor symptoms including anxiety, the so-called wearing-off related anxiety (WRA). Current treatment options are limited and typically focus on either the physical or mental aspects of wearing-off. An integrated approach seems warranted in order to optimally address the complex reciprocal interactions between these aspects. Also, since wearing-off is eventually inescapable, treatment needs to focus on coping, acceptance and self-efficacy. We therefore developed an integrated body awareness intervention, combining principles from physical therapy with acceptance and commitment therapy (ACT) to teach patients to deal with WRA. This study will investigate whether this new intervention, named BEWARE, is more effective in increasing self-efficacy than treatment as usual.

Methods/Design: This is a single-blinded randomized controlled trial in 36 PD patients who experience WRA. Subjects will be recruited from the outpatient clinic for movement disorders of the VU University Medical Center. After providing written informed consent, patients will be randomly assigned to an experimental (BEWARE) or treatment-as-usual (physical therapy) group. Clinical assessments will be performed prior to the intervention, directly after the 6 week intervention period, and at 3-month naturalistic follow up, by a blinded investigator not involved in the study. The primary outcome measure is self-efficacy, while secondary outcomes focus on mobility, daily functioning, anxiety and quality of life.

Discussion: Since wearing-off is an inevitable consequence of levodopa therapy, and current treatment options are insufficient, a multidisciplinary intervention that addresses both physical and mental aspects of wearing-off in PD may foster additional benefits for treating WRA in PD patients over mono-disciplinary care alone.

Trial registration: ClinicalTrials.gov identifier: NCT02054845

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder of the central nervous system with a prevalence of 1.6% among people of 65 years or older [1]. The neurobiological hallmark of PD is a loss of dopaminergic cells, causing the typical motor symptoms such as tremor, rigidity, slowness of movement, postural instability and freezing. Non-motor symptoms, such as autonomic failure, fatigue, depression and anxiety are also prevalent, likely due to an additional involvement of non-dopaminergic systems [2].

To supplement the shortage of dopamine, levodopa treatment is currently the most applied and effective symptomatic treatment [3]. When the dopamine replacement therapy (DRT) takes effect and symptoms become less prominent, the patient is in the 'on' state. In contrast, the state in which the patient is in need of a new dose of dopamine and experiences intensified PD symptoms, is referred to as the 'off'-state. A re-emergence of PD symptoms, shifting from an 'on' state to an 'off' state, is called wearing-off. This typically occurs prior to the next scheduled dose of dopaminergic therapy taking effect [4], and is related to a longer disease duration [5].

Motor and non-motor symptoms have reciprocal influences [6]. About seventy-five percent of patients with motor fluctuations, including wearing-off, experience mood and/or anxiety fluctuations in parallel [7]. This wearing-off related anxiety (WRA) is characterized not only by subjective feelings of anxiety but also by physical complaints, such as sweating, abdominal distress and shortness of breath. Rutten et al [8] showed, by performing a factor analysis on the Beck Anxiety Inventory (BAI), that anxiety symptoms in PD show significant overlap with both autonomic and motor symptoms. This finding demonstrates that physical and mental symptoms are intertwined in PD.

The physical symptoms accompanying WRA are often incongruent with the actual severity and physical impact of motor symptoms of wearing-off, suggesting an increased sensitivity and reactivity to the occurrence of wearing-off symptoms and heightened body awareness in these patients. Body awareness involves an attentional focus on and awareness of internal bodily sensations [9]. An abnormal increase in body awareness can be maladaptive [9] and is, in general, also related to anxiety disorders [10-14].

The anxiety symptoms experienced by PD patients are often responsive to dopaminergic medication [15]. Therefore, the first therapeutic approach for treating

WRA is to optimize the DRT [16]. As the disease progresses, increasing dopaminergic medication (both frequency and dosage) becomes insufficient and complicated due to the increased occurrence of dyskinesias [17]. Also, random fluctuations appear to be more difficult to treat with pharmacotherapeutic approaches since they are unpredictable and not directly related to a lower level of dopamine [17].

Non-pharmaceutical approaches include exercise programs and physical therapy. These have shown to improve motor problems, daily functioning and quality of life in patients with PD [18-21]. While effective for improving mobility-related problems, current physical rehabilitation approaches typically do not offer tools to address the non-motor symptoms of wearing-off.

Cognitive behavior therapy (CBT), mindfulness and acceptance & commitment-based therapies (ACT) have proven to be effective in reducing anxiety symptoms and avoidance behavior in patients with anxiety disorders, also enhancing quality of life [22,23]. Therefore, classic tools from CBT and ACT might be useful in the treatment of the debilitating effects of WRA. A reduction of anxiety symptoms in PD patients is observed in most of the CBT studies [24-26]. However, based on clinical experience, efficacy of classical CBT is limited in PD care, due to the fact that the cognitive methods are suboptimal in addressing the interaction between non-motor and motor symptoms during wearing-off. Moreover, the classical approaches aim to reduce the symptoms, whereas the inevitability of motor and non-motor fluctuations in PD demands the ability to maintain physical and mental balance despite the presence of those fluctuations. This is of great importance mainly in the more advanced stages of PD, where symptom management is more challenging [3]. Therefore, interventions need to focus on independence and self-efficacy more than on reducing symptoms.

To address both the physical and the mental aspects of PD, Wahbeh et al. [27] reviewed mind-body interventions in the treatment of PD and showed that participating in tai chi classes improved the patients' physical condition. Landsman-Dijkstra and colleagues [28] tested a highly structured and standardized 3-day body-awareness program in 14 participants who suffered from chronic non-specific psychosomatic symptoms. An increase of body-awareness, self-efficacy and quality of life was found after the intervention. However, the researchers did not implement a control group in this study.

Mindfulness-based therapies have been proven to be effective in many patient groups, such as patients with chronic pain, anxiety and depressive disorders, by

improving psychological functions and reducing pain and stress [29]. Since PD is a chronic disease and is accompanied by both physical and mental symptoms (motor and non-motor symptoms), combing mindfulness-based therapy with physical rehabilitation might be of potential benefit for PD patients with WRA.

BEWARE is an integrated body awareness intervention, combining acceptance and commitment therapy (ACT), in which mindfulness training is incorporated, with physical therapy. We will test the effectiveness of this intervention (compared with treatment as usual (TAU)) in terms of self-efficacy in PD patients with WRA. We hypothesize that the BEWARE intervention will be more effective in improving self-efficacy than physical therapy alone (TAU).

Methods/Design

Study design

This will be a single-blind randomized controlled trial. Thirty-six PD patients that experience WRA will be randomly allocated to either the BEWARE training group (n=18, 3 groups of 6 patients) or to a control group receiving physical group therapy, which is a usual form of treatment for wearing-off in PD patients at the VU University medical center (n=18, 3 groups of 6 patients). Block-randomization is done using concealed opaque envelopes. All participants are asked to maintain the regular medication schedule during the six-week intervention. Assessments are conducted prior to the intervention, at six weeks directly after the intervention and at 18 weeks follow-up. The assessments will be performed by a blinded investigator who is not involved in the intervention and/or randomization. Figure 1 demonstrates the study design according to the CONSORT statement [30].

Patient recruitment

The patients will be recruited from the outpatient clinic of the VU University medical centre. The neurologists and psychiatrist will be asked to approach PD patients who, in their view, experience WRA. In addition, an announcement will be placed on the website of the Dutch Parkinson patient association (Parkinson Vereniging) and in their magazine. In- and exclusion criteria are listed below.

Patient inclusion criteria

1. Diagnosed with idiopathic PD according to the UK PD Brain Bank criteria [31].
2. Experiencing wearing-off symptoms and/or response fluctuations, as measured with the Wearing-Off Questionnaire 19 [32]. A patient is considered

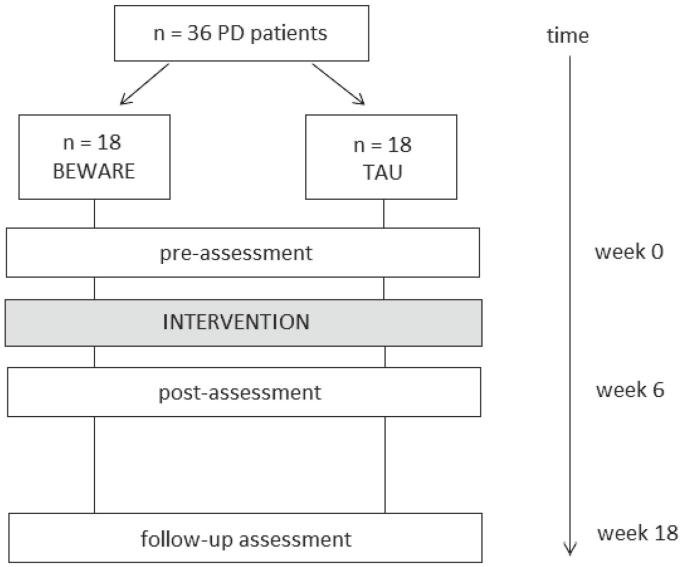

Figure 1. Study flow chart. Abbreviations: BEEWARE = body awareness training; PD = Parkinson's disease; TAU = treatment as usual.

to be experiencing wearing-off if he or she indicates at least one symptom that improves after taking a next medication dose.

3. Presence of clinically relevant anxiety, defined as a Beck Anxiety Inventory score > 26 [33].

Patient exclusion criteria

1. Other neurological, orthopaedic, cardiopulmonary problems that may interfere with participation in the view of the researchers.
2. Cognitive impairment defined as an MMSE score < 24.
3. Insufficient motivation for participation.

Intervention

Two treatment conditions are investigated in this study: the experimental condition (BEWARE) and the TAU (physical therapy). Both interventions consist of 12 sessions, each 1 hour long, 2 times per week for 6 weeks. All treatment sessions occur at the same time of day on the same two days of the week (Monday and Thursday) throughout the study. The treatment groups consist of 6 patients, in both conditions.

Experimental condition: body awareness training (BEWARE)
The experimental intervention is delivered by professionals from the fields of psychology, physical therapy and psychiatry. The BEWARE training is mainly based on the principles of ACT [34]. The goal of this training is to acquire and apply adequate coping strategies with wearing-off, and live a valuable life despite the presence of wearing-off symptoms.

Psycho-education about PD and wearing-off is discussed by the psychiatrist. The psychologist explains and trains the concepts of body awareness, cognitive defusion, valued living and applies imaginary exposure, in ACT therapy known as FEEL (Feeling Experiences Enriches Living) exercises [34]. During the imaginary exposure, patients are asked to imagine a real-life situation that easily triggers wearing-off. The patients practice with experiencing and daring to allow the feelings that are triggered by the 'off' during this imaginary exposure. The patients are encouraged to gradually take part in activities that they previously avoided because of the (anticipation of) wearing-off.

The psychological exercises are alternated by physical exercises that are performed by the physical therapist. These exercises include movement strategies and moving on rhythmic music which helps the patients to relieve stress after the imaginary exposure.

To generalize the intended effect, the patients are given homework assignments, such as body awareness exercises and planning value-based committed actions in daily life.

Control condition: treatment as usual (TAU)
The patients in the control group receive treatment as usual based on the current KNGF guidelines for physical therapy in patients with PD [35]. As in the experimental condition, patients are taught movement strategies.

Outcome measures

Primary outcome measure
The primary outcome measure is self-efficacy, assessed with the 10 item General Self Efficacy Scale (GSES) [36]. Self-efficacy is defined as the extent or strength of one's belief in one's own ability to complete tasks and reach goals, in other words; a person's belief in his or her ability to succeed in a particular situation [37]. In this questionnaire, patients are asked to rate specific statements on a scale from 1 to 4 (1 = not at all true, 2 = hardly true, 3 = moderately true, 4 = exactly true).

Secondary outcome measures

1. The Parkinson's Disease Questionnaire-39 (PDQ-39)

This questionnaire is a measure of quality of life adapted for people with PD [38]. It consists of 39 statements that cover eight domains associated with health, such as mobility and emotionality, that can be influenced by PD. Patients can reply by ticking the relevant answer that indicates whether they experienced problems during the past month (five boxes from 'never' to 'always'). The PDQ-39 is a valid and reliable instrument for patients with PD [38,39].

2. The Wearing-off Questionnaire 19 (WOQ-19)

In this 19 items questionnaire [31], PD patients indicate which symptoms they experience and whether these symptoms improve after administration of PD medication.

3. Beck Anxiety Inventory (BAI)

This self-report questionnaire consists of 21 common symptoms of anxiety [32]. Patients indicate how much they have been bothered by these symptoms during the past week, including today.

4. Beck Depression Inventory (BDI)

This 21-item self-report questionnaire measures whether patients experience depressive symptoms [40]. Patients indicate the statements that are most applicable to their own situation during the past week, including today.

5. 10 Meter Walk Test (10MWT)

To measure comfortable walking speed, the patients are asked to walk 10 metres, which are characterized by a starting and a finishing point [41]. The researcher measures the time needed to cover this distance.

6. Timed One Leg Stance Test (OLST)

This test measures balance by asking the patients to stand on one leg without help [42]. The number of seconds that the patients maintain their balance is noted, with a maximum of 60 seconds.

7. The Nottingham Extended Activities of Daily Living (NEADL) index

This 22-item self-report questionnaire covers four aspects of daily living: mobility, activities in the kitchen, domestic tasks, and leisure activities [43]. Patients indicate whether they independently performed activities during the past weeks.

8. Freezing of Gait (FOG) questionnaire
This 6-item questionnaire is used to identify current problems with walking and symptoms of freezing [44]. For each item patients indicate which of the 5 statements is most applicable.

9. Visual Analogue Scales (VAS)
Before and after each therapy session patients indicate how they are feeling at the actual moment, using 10 VAS. Patients put a cross on a line of 10 cm with extreme feelings at the edges, for example 'relaxed' or 'tense', 'in control' or 'out of control', and 'happy' or 'sad'.

Patient researchers

Since the experimental treatment is a new approach, the opinion and experiences of the participating patients are considered very important. Therefore, two patient researchers of the Dutch Parkinson patient association (Parkinson Vereniging) contribute to the study by anonymously documenting the patients' expectations and evaluation points for qualitative analysis. Prior to, and directly after the intervention period, a semi-structured group interview takes place in which the patients are asked questions related to the study and can share their experiences and suggestions for adaptations in future studies or in the implementation phase. This interview is with the patients (both participants and researchers) only.

Statistical analysis

Calculation of sample size
We expect that the experimental group will show a 10% larger improvement on the GSES after treatment, compared to the TAU group. Based on data on the GSES in other chronic diseases [45], we expect to detect a 10% larger reduction in GSES score from 32 to 28.8 with an overall sd of 3.3. A minimum of 16 patients is required per arm of the trial. With that, including a dropout of 10%, we estimate that 36 PD patients (18 per arm) are needed to achieve a sufficient statistical power of 80% with two-tailed significance level set at $p<0.05$.

Data analysis
To promote data quality, double data entry will be used. Multiple imputation will be applied on missing data. ANOVA with repeated measures will be used for normally distributed outcomes at interval and ratio level. Friedman's non-parametric repeated measures test will be applied for outcomes with non-interval or ratio scale level, or for non-normally distributed variables. Factors in the analysis will be

Group (2 levels: control and experimental) and Time (3 levels: baseline, assessment at week 6 (directly post-treatment) and assessment week 18 (3 month follow up)).

Ethical considerations
Prior to study participation, all patients will be asked to sign a written informed consent. The study was approved by the ethics committee of the VU University medical centre (study number: 13.421).

Data monitoring
The data and safety monitoring board will guard the quality and safety during this study, according to the Good Clinical Practice guidelines.

Discussion (expected results)

Wearing-off is an inevitable and disabling consequence of long-term DRT in patients with PD and WRA is a concept characterized by a complex reciprocal interaction of motor and non-motor symptoms. The general neglect of these complex interactions in the TAU leaves a gap for treatment innovation. BEWARE is a promising therapy for WRA in PD since it specifically focuses on the interaction between physical and mental symptoms. The specific and unique combination of elements of the therapy aim to increase self-efficacy, by strengthening ones own belief to adequately cope with the wearing off and the disproportional concurrent feelings of anxiety, rather than symptom reduction or elimination.

Since the development of wearing-off is associated with long-term treatment of PD with DRT, as well as to an early onset of disease, longer disease duration, and higher doses of levodopa [5,17,46], we will inadvertently include patients that are in a more advanced stage of the disease. Therefore, we must pay specific attention to the potential additional difficulties with patient compliance regarding the amount of effort and commitment we demand from the patients during the twice-weekly intervention.

Based on previous research in combination with our own experience based on a small open pilot study in four PD patients (results not published), we expect to see a significantly bigger improvement in self-efficacy in the BEWARE condition as compared with the TAU condition. A decrease in BAI total score was observed in the patients that participated in the pilot study. The patients in the pilot study reported very positive subjective effects of the intervention. In particular the group aspect

and the holistic approach to address WRA were highly appreciated. Patients stated they were better able to cope with wearing-off after the intervention period. Based on these first experiences, we believe that the BEWARE has the potential to be implemented into health care practices once its value has been established using proper testing with high methodological standards.

Since the wearing-off phenomenon is eventually inescapable, this study is not only of great interest from a patient and caregiver perspective but also from a health care system perspective. Group therapy may lower health care costs compared to individual treatment due to a reduced therapist:patient ratio, and this treatment may allow patients to function longer and in a more independent way in their own home environment.

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8

Body awareness training in the treatment of wearing-off related anxiety in patients with Parkinson's disease: results from a pilot randomized controlled trial

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Abstract

Background: In Parkinson's disease (PD) patients, fluctuations in symptoms commonly occur after many years of dopamine replacement therapy. The so-called wearing-off phenomenon exists of both motor and non-motor symptoms, such as rigidity and anxiety. Current treatment options are limited and an integrated approach is needed to address the complex interactions between motor and non-motor symptoms. Since wearing-off is eventually inevitable, treatment needs to focus on coping, acceptance and self-efficacy. We developed the body awareness training, named BEWARE, combining physical therapy with acceptance and commitment therapy to help PD patients deal better with wearing-off related anxiety (WRA).

Methods: This was an investigator-blinded randomized controlled trial. Forty PD patients with WRA were randomly assigned to the BEWARE or to the treatment as usual (TAU) condition. Assessments were performed prior to and immediately after the treatment period, and at 3-months follow up. The primary outcome was selfefficacy, secondary outcomes focused on mobility, daily functioning, anxiety, depression and quality of life.

Results: There was no significant improvement in self-efficacy in the BEWARE treatment condition when compared to TAU. However, standing balance and emotional wellbeing showed a significant improvement, and feelings of stigmatization showed a trend-significant decrease in the BEWARE condition.

Conclusions: We consider the BEWARE training to be a promising therapeutic approach to address WRA. Improvement points from the participants included 1) less frequent but longer therapy sessions; 2) active involvement of caregivers; and 3) the development of a supportive workbook. The optimized treatment protocol needs further evaluation in a phase III RCT.

Introduction

The typical motor symptoms in Parkinson's disease (PD) include tremor, rigidity, slowness of movement, postural instability, and freezing. Besides these symptoms, PD is accompanied by non-motor symptoms, such as autonomic failure, fatigue, pain, cognitive rigidity, depression and anxiety. Non-motor symptoms often have a higher impact on patients' quality of life than motor symptoms [1]. First line treatment for PD symptoms is dopamine replacement therapy (DRT), e.g., levodopa [2]. In reaction to chronic DRT, PD patients eventually develop response fluctuations, including wearing-off. During wearing-off, both motor and non-motor symptoms can occur and/or become more prominent. Wearing-off is common already at the early stages of PD and is underestimated by routine neurological clinical evaluation. The number of wearing-off symptoms, both motor and non-motor, increases along with disease duration and has a negative impact on quality of life [3].

In PD, motor and non-motor symptoms have reciprocal influences [4]. About 75% of patients with motor fluctuations experience fluctuations in mood and/or anxiety in parallel [5], and anxiety is more common in patients that experience motor fluctuations compared to those who do not [6]. Anxiety associated with wearing-off, referred to as wearing-off related anxiety (WRA), is characterized not only by subjective feelings of anxiety but also by physical complaints, such as sweating, abdominal distress and shortness of breath. According to Rutten et al [7], anxiety symptoms in PD show significant overlap with both autonomic and motor symptoms, which makes it difficult to disentangle them.

The high impact of the physical symptoms accompanying WRA on daily life functioning is often incongruent with the actual severity of the motor symptoms of wearing-off. This suggests heightened body awareness in these patients. Body awareness involves an attentional focus on and awareness of internal bodily sensations [8]. An abnormal increase in body awareness can be maladaptive [8] and is common in anxiety disorders [9]. Normalizing body awareness may therefore help patients to cope with WRA.

A first therapeutic approach to treat WRA is optimization of DRT [10], since the anxiety symptoms experienced by PD patients are sometimes responsive to dopaminergic medication [11-13]. As the disease progresses, this becomes insufficient and is complicated by response fluctuations and increased occurrence of dyskinesias that become unpredictable in nature [14]. Such random fluctuations are difficult to treat with pharmacotherapeutic approaches since they are not directly

related to a low level of dopamine [14]. In addition, treating anxiety symptoms with pharmaceutics, such as psychotropic medication, might interfere with DRT and result in increased tremor or rigidity, which is undesirable.

Non-pharmaceutical approaches to treat wearing-off include exercise programs and physical therapy. These have been shown to improve motor problems, daily functioning and quality of life in PD patients [15-18]. While effective in improving mobility-related problems, current physical rehabilitation approaches typically do not offer tools to address the (interaction with) non-motor symptoms, such as WRA.

Cognitive Behavior Therapy (CBT), mindfulness and Acceptance & Commitment-based therapies (ACT) are effective in reducing anxiety symptoms, distress and avoidance behavior and enhancing quality of life in patients with anxiety disorders and PD [19-23]. Therefore, tools from CBT and ACT might also be useful in the treatment of the debilitating effects of WRA in PD. However, the classical approach aims to reduce symptoms, whereas the inevitability of motor and non-motor fluctuations in PD demands a coping strategy on dealing with these fluctuations. In addition, cognitive rigidity becomes more prominent with disease progression and complicates a mono-disciplinary cognitive treatment approach.

To address both the physical and the mental aspects of PD, Wahbeh et al. [24] reviewed mind-body interventions in the treatment of PD and showed that participating in tai chi classes improved the patients' physical condition. Landsman-Dijkstra and colleagues [25] tested a highly structured and standardized 3-day body-awareness program in 14 participants who suffered from chronic non-specific psychosomatic symptoms. After the intervention body awareness, self-efficacy and quality of life had significantly improved. The main limitation of this study, apart from the small sample size, was the lack of a control group. In summary, mind-body interventions seem promising for the treatment of WRA in PD patients, but the therapeutic efficacy has yet not been investigated.

We therefore developed an integrated body awareness training combining ACT with physical therapy for patients with PD, named BEWARE. We investigated the feasibility and the efficacy of this group intervention using a pilot randomized controlled study, with conventional group physical therapy as active control condition.

Methods

For a detailed description of the methodology, including the intervention protocol, we refer to the article of Ghielen et al. [26].

Study design

We conducted an investigator-blind randomized controlled trial. Forty PD patients with WRA were randomly allocated to either the BEWARE training (4 groups of 4-6 patients) or to the treatment as usual (TAU) receiving group physical therapy (4 groups of 4-6 patients). Block-randomization with 2 blocks of 4 was done using concealed opaque envelopes and conducted by an independent investigator. Assessments were conducted prior to the intervention (baseline), directly after the six-weeks intervention (post-treatment) and at 18 weeks follow-up (3 months after completing the intervention). A blinded investigator, who was not involved in the intervention and/or randomization, performed all assessments.

Patients

Forty participants were recruited from the outpatient clinic of the VU university medical center and through the Dutch Parkinson patient association (see figure 1 for the flow chart according to the CONSORT-statement [27]). Inclusion criteria were: 1) a diagnosis of idiopathic PD according to the UK PD Brain Bank criteria [28]; 2) the presence of one or more wearing-off symptoms, as measured with the 19-item Wearing-Off Questionnaire (WOQ-19) [29]; 3) clinically relevant anxiety, defined by a Beck Anxiety Inventory (BAI) score >26. Patients with cognitive impairment defined as a Mini Mental State Examination (MMSE) score of <24, insufficient motivation for participation, or neurological, orthopaedic or cardiopulmonary problems that could interfere with participation in the view of the researchers, were not eligible for participation. The patients were asked to maintain a stable medication schedule throughout the treatment period of six weeks. To detect a 10% larger reduction in the General Self Efficacy Scale (GSES) in the BEWARE condition compared to TAU, a minimum of 16 patients was required per treatment condition to achieve a statistical power of 80% with a two-tailed significance level set at $p<0.05$. Considering a maximum dropout of 10%, 36 PD patients (18 per condition) were needed.

Interventions

Two treatment conditions were investigated in this study: the experimental condition (BEWARE) and the conventional physical therapy (TAU). Both interventions consisted of 12 sessions, each 1-hour long, 2 times per week for 6 weeks. Each group consisted

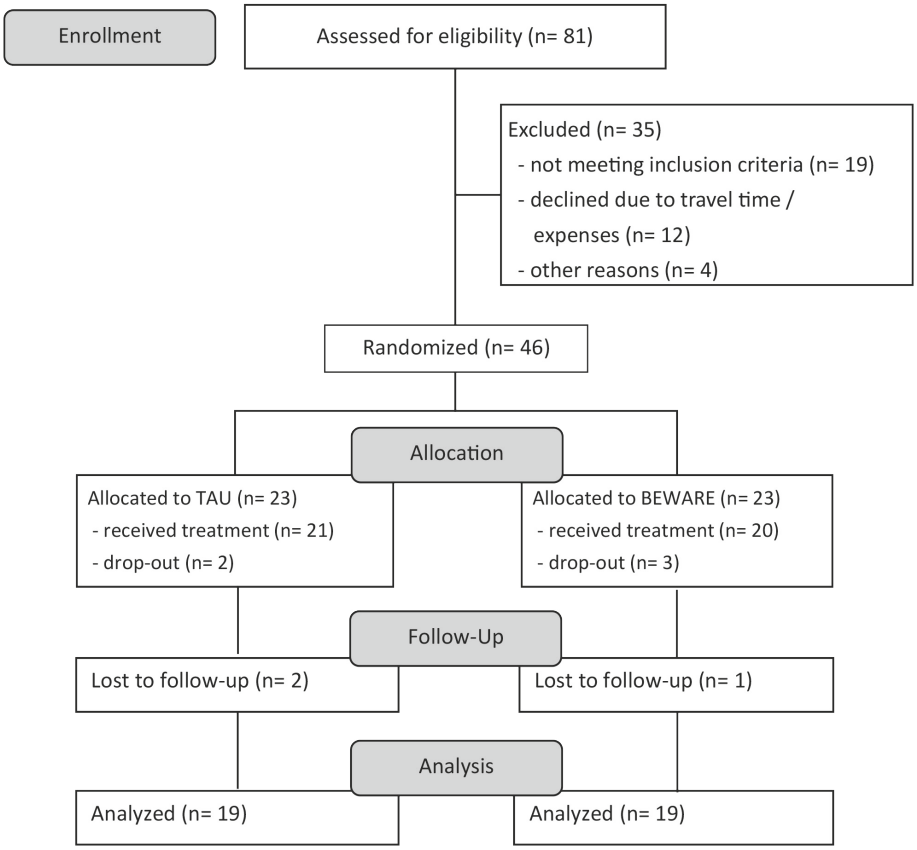

Figure 1. Study flow chart

of 4-6 patients. All treatment sessions occurred at the same time on the same two days of the week (Monday and Thursday) throughout the study.

Experimental condition: body awareness training (BEWARE)

The experimental intervention was delivered in a group setting by professionals from the disciplines psychology, physical therapy and psychiatry. The BEWARE training is mainly based on the principles of ACT [30]. The goal of this training is to acquire and apply adequate coping strategies with wearing-off, and live a valuable life despite the presence of wearing-off symptoms. The intervention consists of the following elements: psycho-education, training in ACT, imaginary exposure using FEEL (Feeling Experiences Enriches Living) exercises, diminishing avoidance behaviour, physical exercises and homework assignments. Homework assignments

included inventory and planning of value-based committed actions and performing mindful body scans.

Control condition: treatment as usual (TAU)

The patients in the control group received TAU based on the current Royal Dutch Society guidelines for physical group therapy in patients with PD, consisting of movement strategies for improving balance, gait, transfers and posture [31]. No homework assignments were assigned in this condition.

Ethical considerations

Prior to study participation, all patients were asked to sign a written informed consent. The study was approved by the ethics committee of the VU university medical centre (study number: 13.421). Trial registration: ClinicalTrials.gov identifier: NCT02054845.

Outcome measures

Primary outcome measure

The primary outcome measure was self-efficacy, assessed with the 10 item GSES [32]. Self-efficacy is defined as the extent or strength of one's belief in one's own ability to complete tasks and reach goals [33]. In the GSES, patients are asked to rate 10 specific statements on a scale from 1 to 4, with a higher rating representing better self-efficacy.

Secondary outcome measures

We measured symptoms of wearing-off by means of the WOQ-19, in which patients can check 19 symptoms they experience and indicate whether these symptoms usually improve after their next medication dose [29]. The BAI (range 21-84) [34] and the Beck Depression Inventory (BDI; range 0-63) [35] were used to measure anxiety and depressive symptoms, respectively. A higher score on these questionnaires indicates more (severe) symptoms. The Parkinson's Disease Questionnaire-39 (PDQ-39) was used to assess quality of life, which contains the subscales mobility, activities of daily living, emotional wellbeing, stigma, social support, cognitions, communication, and bodily discomfort [36]. Higher scores on these subscales indicate more (severe) symptoms, e.g. lower quality of life. We measured activities of daily living with the Nottingham Extended Activities of Daily Living (NEADL) index [37]. A higher score represents more independence in performing daily life activities. To assess symptoms of freezing the Freezing of Gait (FOG) questionnaire was used, where a higher score represents more severe freezing [38]. The 10 Meter Walk Test

(10MWT) [39] and the Timed One Leg Stance Test (OLST) [40] were used to assess walking speed and standing balance, respectively.

Qualitative evaluation

Since the experimental treatment was a new approach, the opinion and experiences of the participating patients were considered very important. Therefore, two patient researchers of the Dutch Parkinson patient association (Parkinson Vereniging) contributed to the study by providing input in the design phase and by conducting a group interview on the patient's expectations at baseline and evaluation points at post-treatment. These interviews were in the absence of the academic employees and were documented anonymously for qualitative analysis. We thought that the participants felt more comfortable to address critical feedback points anonymously and towards the patient researchers, compared to the researchers.

Data analysis

The means, standard deviations, and ranges of the descriptive measures were calculated. Differences in demographic, disease related, and outcome measures were investigated using independent t-tests or Mann-Whitney U tests, and chi-square tests where appropriate. Linear mixed model analyses were used to estimate the effect of BEWARE (compared to TAU) on the outcome measures. Besides an overall intervention effect, the separated effects at both post-treatment and follow-up were estimated. For the latter, time and the interaction between condition and time were added to the model. We corrected for baseline differences in all analyses, also when baseline measures did not significantly differ between conditions. The intervention effect was estimated by the regression coefficient (β) and its related p-value. The significance level was set at a p-value of 0.05, two-tailed. In addition, we separately included covariates such as cognition, anxiety, LEDD score, and number of wearing-off symptoms at baseline as interaction-effects (with condition) in the model to investigate whether they were of significant influence on the intervention effect. These results can help to indicate for whom the BEWARE treatment is most effective.

Results

Participant characteristics

Table 1 shows the descriptive statistics of the 38 patients that completed the study, per condition. No significant baseline differences between the two conditions were found on demographic, disease related, or outcome measures. All participants had

a Hoehn & Yahr (H&Y) staging of 2 or 3 in the ON stage, as retrospectively assessed by the physical therapists. We assessed this retrospectively over 12 treatment sessions to obtain a reliable indicator of the disease stage, since H&Y scores are dependent on the (moment of the) day. Twelve patients, six in each condition, used pharmacotherapy for anxiety and/or depressive symptoms during the study (see table 1). There was a non-selective drop-out of 26%, which was mainly due to the burden related to the frequency of therapy sessions (including travel distance).

Outcomes

In table 2 the means and standard deviations of the outcome measures are shown, per group treatment.

Primary outcome: There was no significant differential treatment effect over time on the primary outcome measure 'self-efficacy' (see table 3).

Secondary outcomes: There was a significant improvement in emotional wellbeing, as measured with the PDQ-39, in the BEWARE condition compared with the TAU condition, both at post-treatment and at follow-up. In addition, the timed balance test significantly improved with the BEWARE training compared with the TAU, also both at post-treatment and at follow-up. The regression coefficient of the stigmatization subscale of the PDQ-39 showed a trend-significant improvement in the BEWARE condition compared to the TAU condition. Figure 2 illustrates the changes over time, separately for the two conditions.

Covariates

Severity of wearing-off, represented by the number of wearing-off symptoms that patients reported at baseline, the level of anxiety, represented by the BAI total score, and the LEDD score, did not influence the effect of the intervention. However, cognitive status, represented by the MMSE total score, modulated the treatment effect for depressive symptoms (BDI): patients that had a higher score on the BDI, but were cognitively most intact, showed larger improvements after the BEWARE treatment. Besides this finding, the MMSE score had a significant influence on the intervention effect for freezing-of-gait ($p=0.009$), quality of life (PDQ) - emotional wellbeing ($p=0.045$), PDQ - social support ($p=0.049$), activities of daily living (NEAI) – household ($p=0.047$), and NEAI - leisure time ($p=0.026$).

Table 1. Descriptive statistics of the participants per condition. Demographic and clinical characteristics are included.

	TAU (n = 19)			**BEWARE (n = 19)**			**Difference**
	mean	*standard deviation*	*range*	*mean*	*standard deviation*	*range*	*p-value*
% female	45			35			0.35
age (yr)	66,6	8,4	48-80	59,6	9,7	34-74	0.19
LEDD score	1340	534	660-2547	1165	405	420-1946	0.42
Use of psychotropic medication (number of patients)	6			6			
disease duration (yrs)[@,#]	12,3	4,3	5-20	10,5	5,7	1-24	0.25
Hoehn & Yahr stage in ON[@]			2-3			2-3	0.29
side of onset (% left)[@,#]	56			57			0.96
anxiety (BAI total score)	39,1	9,2	23-57	40,5	13,7	21-65	0.70
cognition (MMSE total score)	27,5	1,9	24-30	28,1	1,6	24-30	0.33
wearing-off symptoms (amount)			1-16			1-18	0.96

TAU = Treatment As Usual; BAI = Beck Anxiety Inventory; BEWARE = body awareness intervention; LEDD = Levodopa Equivalent Daily Dose; MMSE = Mini Mental State Examination

[@] retrospectively assessed

[#] assessed in a subsample of participants (n = 30)

Table 2. Group means and standard deviations of the participants that completed the study.

Outcome measure	TAU (n = 19)			BEWARE (n = 19)		
	baseline	*posttreatment*	*follow-up*	*baseline*	*posttreatment*	*follow-up*
GSES [0-40]	28,50 (4,56)	28,56 (4,27)	30,75 (4,78)	30,75 (5,70)	30,93 (3,56)	31,57 (7,00)
BAI [21-84]	39,05 (9,23)	39,25 (9,43)	36,69 (6,05)	40,47 (13,71)	35,69 (12,14)	36,67 (9,85)
BDI [0-63]	12,30 (8,39)	12,44 (5,41)	9,81 (8,52)	9,80 (7,63)	9,07 (6,01)	10,47 (7,76)
PDQ-mobility [%]	48,55 (19,01)	45,78 (18,18)	45,00 (21,95)	38,55 (19,58)	37,50 (21,13)	40,67 (21,35)
PDQ-activities of daily living [%]	33,99 (17,14)	33,59 (20,44)	34,64 (24,33)	36,57 (18,22)	32,78 (19,21)	32,14 (19,30)
PDQ-emotional wellbeing [%]	40,28 (21,10)	40,10 (17,93)	35,16 (15,95)	32,02 (19,89)	26,94 (19,15)	21,73 (19,35)
PDQ-stigma [%]	30,00 (16,91)	26,17 (20,18)	30,08 (19,53)	22,06 (18,89)	22,92 (21,48)	19,17 (22,34)
PDQ-social support [%]	25,42 (18,82)	23,44 (17,80)	23,81 (18,74)	24,48 (18,63)	21,11 (21,33)	22,22 (18,00)
PDQ-cognitions [%]	33,44 (17,36)	33,98 (17,53)	36,33 (17,71)	34,38 (17,18)	33,33 (16,65)	34,17 (17,66)
PDQ-communication [%]	32,50 (22,28)	31,77 (19,77)	36,98 (19,24)	27,19 (15,43)	26,67 (19,21)	25,00 (16,96)
PDQ-bodily discomfort [%]	53,33 (24,24)	61,98 (16,38)	52,08 (18,88)	44,30 (22,92)	42,86 (27,12)	50,00 (30,37)
NEAI-mobility [6-24]	20,05 (3,33)	20,25 (3,91)	20,50 (4,18)	21,10 (4,38)	22,40 (2,92)	21,87 (4,02)
NEAI-kitchen [5-20]	17,70 (2,89)	17,44 (2,42)	18,19 (2,79)	17,45 (4,55)	18,47 (3,70)	18,00 (3,74)
NEAI-domestic [5-20]	15,35 (3,84)	15,31 (4,06)	15,75 (4,06)	15,35 (4,33)	16,27 (3,49)	15,73 (4,37)
NEAI-leisure [6-24]	17,84 (4,41)	18,25 (5,00)	18,06 (5,80)	18,83 (4,78)	19,33 (4,08)	19,53 (4,03)
10MWT speed [s]	9,85 (2,62)	9,16 (1,60)	8,86 (1,95)	8,59 (1,91)	8,44 (1,44)	8,49 (1,45)
10MWT steps [#]	16,56 (3,28)	15,48 (2,84)	15,40 (2,72)	14,86 (2,41)	14,32 (1,82)	14,57 (2,14)
OLST left [s]	15,66 (17,89)	18,08 (16,51)	14,80 (15,88)	27,97 (23,28)	33,89 (26,22)	31,64 (23,94)
OLST right [s]	18,12 (20,05)	22,50 (22,78)	15,99 (16,39)	26,91 (23,70)	40,67 (22,59)	34,06 (24,73)
FOGQ [0-24]	11,60 (4,63)	12,56 (5,54)	12,94 (5,41)	9,15 (4,72)	9,67 (6,32)	9,60 (4,93)

Abbreviations: TAU = Treatment As Usual; BEWARE = body awareness intervention; GSES = General Self Efficacy Scale; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; PDQ = Parkinson's Disease Questionnaire; ADL = Activities of Daily Living; NEAI = Nottingham Extended Activities of daily living Inventory; 10MWT = 10 Meter Walk Test; OLST = One Leg Stance Test; FOGQ = Freezing of Gait Questionnaire.

Table 3. Treatment effects (overall, at posttreatment and at follow-up) using mixed model analyses.

Outcome measure	Overall treatment effects			Posttreatment effects			Follow-up effects		
	β	95% CI	Significance level	β	95% CI	Significance level	β	95% CI	Significance level
GSES [0-40]	-0,38	-2,45 – 1,70	p=0,714	-0,45	-2,89 – 1,99	p=0,712	-0,13	-2,58 – 2,33	p=0,919
BAI [21-84]	-3,29	-8,03 – 1,45	p=0,166	-2,86	-7,55 – 1,82	p=0,222	-2,95	-7,70 – 1,80	p=0,216
BDI [0-63]	1,49	-0,78 – 3,77	p=0,189	0,77	-1,79 – 3,33	p=0,549	2,17	-0,39 – 4,73	p=0,095
PDQ-mobility [%]	3,00	-6,43 – 12,44	p=0,519	1,53	-8,27 – 11,34	p=0,753	-6,13	-22,57 – 10,31	p=0,451
PDQ-ADL [%]	-0,57	-10,88 – 9,74	p=0,911	-0,36	-11,01 – 10,29	p=0,946	-1,45	-12,47 – 9,56	p=0,785
PDQ-emotional wellbeing [%]	-10,89	-18,78 – -3,00	p=0,009**	-9,46	-17,81 – -1,11	p=0,028*	-15,56	-27,81 – -3,31	p=0,016*
PDQ-stigmatization [%]	-8,18	-17,43 – 1,07	p=0,081	-5,47	-15,34 – 4,41	p=0,270	-8,84	-21,00 – 3,31	p=0,145
PDQ-social [%]	-3,58	-10,20 – 3,04	p=0,277	-5,34	-13,18 – 2,50	p=0,177	-13,85	-26,00 – -1,70	p=0,028*
PDQ-cognition [%]	-1,27	-7,64 – 5,09	p=0,685	-1,75	-8,40 – 4,91	p=0,598	-4,88	-14,78 – 5,02	p=0,314
PDQ-communication [%]	-4,87	-13,24 – 3,50	p=0,243	-3,95	-12,81 – 4,90	p=0,372	-11,20	-19,28 – -2,48	p=0,014*
PDQ-physical discomfort [%]	0,95	-10,08 – 11,98	p=0,861	-3,43	-15,34 – 8,49	p=0,564	3,87	-10,99 – 18,72	p=0,594
NEAI-mobility [6-24]	0,34	-1,55 – 2,24	p=0,713	0,61	-1,37 – 2,59	p=0,534	-0,60	-3,03 – 1,84	p=0,613
NEAI-kitchen [5-20]	0,16	-1,64 – 1,96	p=0,858	0,43	-1,46 – 2,32	p=0,647	1,05	-1,54 – 3,63	p=0,404
NEAI-domestic [5-20]	0,36	-0,93 – 1,65	p=0,569	0,62	-0,83 – 2,07	p=0,394	0,70	-1,73 – 3,14	p=0,556
NEAI-leisure [6-24]	0,15	-2,06 – 2,35	p=0,893	0,16	-2,42 – 2,74	p=0,899	2,60	-1,60 – 6,81	p=0,212
10MWT speed [s]	-0,42	-1,43 – 0,59	p=0,400	-0,41	-1,48 – 0,67	p=0,451	-1,41	-3,53 – 0,71	p=0,180

Table 3. Treatment effects (overall, at posttreatment and at follow-up) using mixed model analyses. (continued)

Outcome measure	Overall treatment effects			Posttreatment effects			Follow-up effects		
	β	95% CI	Significance level	β	95% CI	Significance level	β	95% CI	Significance level
10MWT steps [#]	-0,57	-2,20 – 1,06	p=0,480	-0,70	-2,39 – 0,99	p=0,407	-0,88	-4,38 – 2,63	p=0,604
OLST left [s]	7,65	-2,84 – 18,14	p=0,147	9,08	-2,29 – 20,46	p=0,114	11,10	-8,03 – 30,22	p=0,239
OLST right [s]	12,06	0,83 – 23,30	p=0,036*	16,10	3,71 – 28,50	p= 0,012*	18,32	0,24 – 36,40	p=0,047*
FOGQ [0-24]	-0,01	-2,03 – 2,01	p=0,993	0,03	-2,13 – 2,18	p=0,980	-1,26	-4,25 – 1,73	p=0,387

*TAU = Treatment As Usual; BEWARE = body awareness intervention; GSES = General Self Efficacy Scale; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; PDQ = Parkinson's Disease Questionnaire; ADL = Activities of Daily Living; NEAI = Nottingham Extended Activities of daily living Inventory; 10MWT = 10 Meter Walk Test; OLST = One Leg Stance Test; FOGQ = Freezing of Gait Questionnaire; β = regression coefficient, 95% CI = 95% confidence intervals; * = p<0.05; ** = p<0.001.*

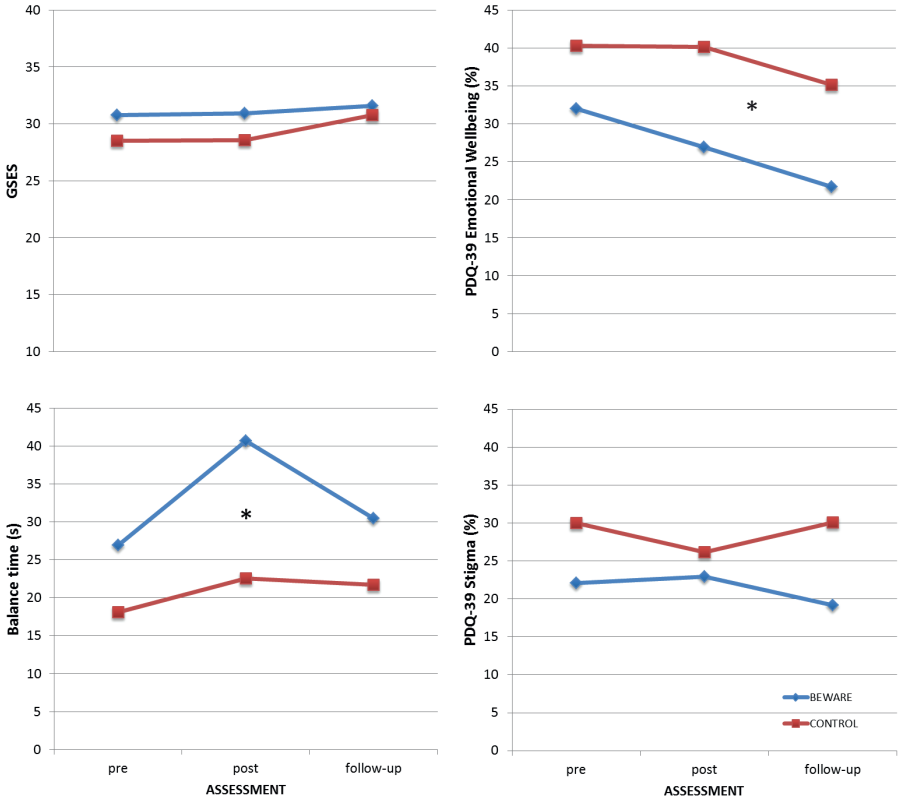

Figure 2. Graphical representation of interesting outcome measures.

*Abbreviations: GSES = General Self Efficacy Scale, PDQ-39 = Parkinson's Disease Questionnaire – 39 items, BEWARE = body awareness intervention, CONTROL = treatment as usual, * = significant overall treatment effect.*

Qualitative analysis

The patient researchers systematically documented the patients' evaluations and revealed that the majority (84%) of patients that participated in the BEWARE treatment group experienced the new treatment as positive. Eight (21%) participants found it burdensome to visit the outpatient clinic twice every week. For future adaptation of the intervention, the patients suggested to lower the frequency (e.g. once instead of twice per week) but increase the duration (e.g. one and half hour instead of one hour) of the therapy sessions. In addition, all patients suggested to more actively involve partners/caregivers and to develop a tool to keep managing WRA and applying the principles learned during the sessions in the home-environment during and after treatment completion (e.g. with self-help material).

Discussion

This pilot randomized controlled phase II study investigated a newly developed intervention involving body awareness training (BEWARE) for WRA in patients with PD. Patients that participated in the BEWARE treatment (compared with TAU) showed improved emotional wellbeing as well as standing balance, both at post-treatment and follow-up. Feelings of social stigmatization trend-significantly decreased in the BEWARE condition compared with the TAU condition.

The BEWARE treatment was not superior to TAU with regard to the primary outcome measure self-efficacy (GSES). One explanation involves the content of the BEWARE intervention, that will be further optimized. The efficacy of the treatment might increase by removing or adjusting exercises that appeared less applicable to WRA according to the therapists. Since roughly half of the time of each BEWARE treatment session focused on ACT principles, instead of physical exercises as in the TAU condition, the treatment contrast regarding time that is spent on coping with WRA between the two conditions might not have been large enough to achieve significant between group differences in self-efficacy. In addition, based on the experience and feedback of participants, the frequency of the intervention sessions could be reduced while the duration of each session should be increased to improve feasibility and compliance. Also, more home-assignments or tools should be developed to achieve a better implementation of the principles in daily life.

Another explanation might be that the GSES is not responsive enough to measure changes in coping-related aspects of WRA in patients with PD. Certain self-efficacy beliefs that relate to *controlling* the disease and its symptoms may be unhelpful in the context of WRA, as Dennison and colleagues [41] also argue in a review of psychological correlates of adjustment in patients with multiple sclerosis. Critical review of the GSES reveals that while several items focus on dealing with unexpected situations, other statements in the questionnaire involve problem *solving*. In an ACT-based intervention like BEWARE, the effect might be measured better by specifically focusing on the subject's perceived capability to *deal* with WRA, instead of solving or controlling the situation. Since patients are taught to focus on what they find important, despite of their illness, another questionnaire might be more applicable and sensitive to change. While no such specific questionnaire is currently available nor validated for PD, one may consider the Engaged Living Scale [42] or the Goal Attainment Scaling [43]. These questionnaires focus on personal goals and values, which may be more closely related to the main focus of the BEWARE treatment, but would need to be validated in PD prior to implementation in a follow up study.

The BEWARE treatment did improve emotional wellbeing, which is well explained by the psychological principles of ACT. The valued living exercises may have resulted in an attitude shift in the patients, now focusing more on what is important for them and trying to live life according to those positive values. Another possibility is that the body awareness exercises might have normalized the patients' awareness of internal body sensations so that the perceived impact and actual severity of motor symptoms are more congruent, resulting in a less stressful experience during wearing-off. The improvement in standing balance might be explained by the additional physical therapy components. The combination of physical and mental components in the BEWARE treatment might have increased patients' balance confidence, which could have improved their standing balance. Since this improvement was superior to the TAU group, the improvement in mental state might have been beneficial, due to strong reciprocal interactions between physical and mental symptoms. The connection between an improved mental state and balance is, however, not yet been investigated. Future research should therefore include the falls efficacy scale to assess fear of falling and relate this outcome to psychological outcomes [44].

Although feeling stigmatized did not show a statistically significant reduction in the BEWARE condition compared with the TAU condition, the regression coefficient is of potential interest for future investigation, especially at follow-up (table 3). The items of the stigma subscale of the PDQ-39 assess avoidance behavior and the experience of being in public places in the context of the disease. Reducing avoidance behavior is being specifically addressed in the BEWARE treatment, using FEEL exercises. A recent review [45] states that a more avoidant personality predicts heightened anxiety in PD patients. The fact that the stigma subscale shows an improvement only at trend-level might be explained by the limited number of items, also not covering the whole spectrum of stigmatization. In addition, the treatment and follow-up duration might not have been long enough to measure a longer term decrease in avoidance behavior and social distress related to disease characteristics.

The BEWARE treatment seemed to be most beneficial for patients that were emotionally most affected (e.g. higher BDI score), but were cognitively most intact. Therefore, patients should be better screened on cognitive dysfunction before starting an adapted and improved BEWARE treatment study. In addition, because of the small sample size, this result needs to be further investigated in a larger (multi-center) study sample.

The number of wearing-off symptoms at baseline did not seem to influence the treatment effect. However, the number of wearing-off symptoms might not be a good criterion to assess the severity of the wearing-off, since patients may experience just one but very disabling wearing-off symptom versus several, less disabling wearing-off symptoms. The severity of discomfort, instead of the number of symptoms, is not included in the WOQ-19. In the future it might be better to use other measures to assess disease severity, such as the Movement Disorder Society-Unified Parkinson's Disease Scale (MDS-UPDRS) part III and IV [46], in combination with times of medication intake.

Results from the qualitative analysis indicate that the burden of the frequency of therapy sessions was high for several patients while the duration of each session could be increased. In addition the involvement of caregivers was missed. In a follow-up study, the frequency of therapy sessions should be reduced (to once a week), while the length of the sessions can be extended to one and half hour. In addition, more homework with proper monitoring can be implemented to promote implementation of the treatment principles in daily life, and the addition of 1 or 2 home sessions also involving the partner and/or the caregiver might add to the long-term effects of the intervention. In addition, a booster session at 12 weeks after treatment completion might also facilitate better implementation into daily life and long-term effects, as is also argued by Morris and colleagues [47]. Self-help material should be developed so that patients have something they can fall back on at home in between sessions and after completion of the training. Concerning the content of the BEWARE training, more time will be spent on exercises concerning valued living and less time will to be spent on repetition of previously trained elements. Homework will focus more on the involvement of the patients' daily life (motor and non-motor) struggles, and the amount of homework will be increased with the goal to perform one exercise with a duration of 10-15 minutes every day. In addition, cognitive demands will be decreased by focusing more on the body and daily life activities, and by more repetition using the self-help material and a booster session.

A major strength of this study is the implementation of a TAU group, which controlled for the physical therapy elements that were also implemented in the BEWARE group. The additional effect of the psychological elements was therefore investigated. This was the first time this new approach to the treatment of PD patients with wearing-off, which includes both psychological and physical elements, was investigated. The number of participants, although calculated prior to study set-up, could have been insufficient to achieve sufficient statistical power, which can be considered a limitation.

In conclusion, this pilot randomized controlled study provided preliminary evidence that the BEWARE treatment, as compared with conventional physical therapy, is a promising therapeutic approach to address WRA. In its current form, the BEWARE training is most effective in patients with healthy cognition. The results provide important clues to optimize the BEWARE treatment protocol for testing in a future large-scale clinical trial, which is necessary to underpin its added therapeutic value before future implementation can be considered.

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9

General discussion

In clinical practice, patients with PD often present a complex variety of symptoms. Although PD is classified as a movement disorder, non-motor symptoms (including anxiety) are an important elements of the disease. In this thesis, it is hypothesized that in PD patients motor and non-motor symptoms have reciprocal influences and interact with one another, complicating diagnosis and treatment.

In the first part of this thesis (**chapters 2 - 5**) we focused on the associations and complex interactions between anxiety, other non-motor symptoms and motor symptoms in PD. We used the findings from these chapters, together with clinical experience and other research in the field, to develop a potentially better, multidisciplinary treatment for wearing-off related anxiety in PD. In the second part (**chapters 6 - 8**) we focused on the efficacy of psychological and multidisciplinary treatment of motor and non-motor symptoms in PD.

In the sections below, I summarize the results of each chapter of this thesis. Several methodological strengths and limitations of our work are considered, as well as the clinical implications of our findings. Finally, I discuss directions for future research and final conclusions.

Summary of the results

In **chapter 2** we investigated the phenomenology of anxiety in PD by performing a principal component analysis to explore underlying symptom dimensions of anxiety as measured with the Beck Anxiety Inventory (BAI) [1]. We showed that the BAI consists of one affective and four somatic anxiety symptom subscales. We found significant associations between the somatic subscales and motor and autonomic symptoms, whereas the affective subscale showed a significant association with depressive symptoms and no association with motor or autonomic symptoms. The total BAI score also showed a significant association with severity of depressive symptoms.

To investigate the generalizability of the findings in chapter 2, in **chapter 3** we replicated these findings using a principal component analysis on the BAI in PD patients that were referred for neuropsychiatric assessment [2]. Again, we found one affective and four somatic anxiety symptom subscales, and a strong association between anxiety and depression. In a post-hoc analysis, the score on the affective subscale showed equal predictive value as compared to the total BAI score in predicting whether or not patients received an anxiety disorder diagnosis through psychiatric evaluation.

In **Chapter 4** we used an explorative network analysis to study the associations between motor and anxiety symptoms, comparing symptom networks of high-anxious versus low-anxious PD patients. We investigated whether anxiety and motor symptoms are more strongly connected in the high-anxiety PD patient group, compared to the low-anxiety PD patient group [3]. The high-anxiety PD patient network showed higher global strength. In spite of group differences in which the high-anxiety group showed significantly worse motor and cognitive function, a higher age, and included more female patients, the network comparison test showed a significant difference in global strength, but did not show statistically significant differences in strength of the connections between motor and anxiety symptoms between the patient groups.

Chapters 2,3, and 4 focused on the associations between motor, anxiety, and other symptoms, not taking into account their temporal relationships. In **chapter 5**, we investigated the longitudinal associations between anxiety, fear of falling, and freezing of gait in 153 PD patients [4]. Across 4 measurements, with three weeks between each measurement, all associations were significant, with the strongest association between fear of falling and freezing of gait. Adjustments for disease characteristics and adverse effects of medication diminished all associations.

After a description of the phenomenology of anxiety, and its cross-sectional and longitudinal associations with motor and other non-motor symptoms, part 2 of this PhD thesis focusses on the treatment of these complex symptom interactions in PD patients.

In **chapter 6**, we describe two meta-analyses on the effects of cognitive behavioral and mindfulness-based therapies on psychological distress in patients with neurodegenerative disorders [5]. The included studies were divided in those comparing the treatment of interest with an active control condition and those with a treatment as usual or waitlist control condition. The results showed that psychological interventions have a small to moderate effect on reducing psychological distress in patients with PD and Multiple Sclerosis (MS). The overall quality of the included studies was low and showed considerable heterogeneity. No evidence was found for publication bias.

Chapters 7 & 8 present the study protocol and results of a pilot randomized controlled trial (RCT) in which we described and investigated a newly developed multidisciplinary group treatment for wearing-off related anxiety in PD named *BEWARE* [6, 7]. *BEWARE* is a body awareness group training in which we combine

elements from Acceptance and commitment therapy (ACT) with physical therapy. We compared the *BEWARE* training with group physical therapy. In **chapter 8** we describe the results of this pilot RCT. Patients that participated in the *BEWARE* training showed no significant improvement in the primary outcome measure, self-efficacy, compared to the control condition. Patients that received the *BEWARE* training (more than patients that received physical therapy only) showed improved emotional wellbeing as well as standing balance, both at post-treatment and follow-up. Feelings of social stigmatization decreased in this group as well, however, this was not statistically significant.

General reflection and clinical implications

In **chapters 2 and 3**, we describe the overlap between anxiety, depression, autonomic failure and motor dysfunction in different PD patient populations [1, 2]. Autonomic and motor symptoms were associated with the somatic subscales of the BAI, while depressive symptoms were associated with the affective subscale. The network analysis presented in **chapter 4** also showed connections between symptoms of motor failure and anxiety. This gives rise to the question whether motor and (somatic) anxiety symptoms often co-occur, or that these items show overlap because they measure one and the same symptom. For example, somatic symptoms such as trembling and feeling unsteady can be interpreted both as motor symptoms of PD and as somatic equivalents of anxiety. This complicates diagnosing anxiety in PD, which can lead to either under- or overdiagnosis, since the somatic symptoms can both be interpreted as either PD-related or as anxiety-related. Within the explorative network analysis, the overlap between motor symptoms and somatic anxiety symptoms was present in both patient groups, in spite of the level of anxiety. This argues in favour of the hypothesis that the specific somatic anxiety and motor symptom scores represent one and the same symptom. To eliminate room for interpretation and measure anxiety without somatic equivalents, one could advise to solely use the 7-item *affective* subscale of the BAI that does not include motor aspects, as presented in **chapter 2 and 3** [1, 2]. This subscale showed equal predictive value as compared to the total BAI in whether or not patients received an anxiety disorder diagnosis through psychiatric evaluation. However, despite of its equal predictive power, we do not recommend to disregard the somatic symptoms completely, as they are also an important part of anxiety [8]. The *affective* subscale might be useful as a first screening tool for anxiety in PD, to then interpret anxiety symptoms in the context of motor and autonomic symptoms.

Chapters 2,3, and 4 described analyses on cross-sectional data, however, symptom fluctuations over time are very much apparent in PD patients. Over 65% of PD

patients experience motor fluctuations within 5 years of dopamine replacement therapy [9]. With these motor fluctuations, another 75% of PD patients experience mood and anxiety fluctuations in parallel [10]. Motor and anxiety symptoms might interact over time, so longitudinal data may represent the interplay between these symptoms better than cross-sectional data. In **chapter 5** we showed that motor and anxiety symptoms influence one another over time, in which fear of falling and potentially anxiety precede freezing of gait. In addition, medication and its adverse effects (including fluctuations) seem to influence both freezing of gait and anxiety symptoms as well as their association, which is in line with previous research [11]. Motor and anxiety symptoms can co-occur simultaneously, as is shown in **chapters 2,3, and 4**. These symptoms might originate in a subsequent manner over time, possibly creating a vicious cycle, which is indicated by our longitudinal analysis in **chapter 5**. This is also what is seen in clinical practice, and is evidenced by previous research [12, 13]. This vicious cycle can be a process that takes place within minutes [14] and we only investigated the symptom interactions over a time-period of a few weeks. Our results indicate that anxiety can have an impact on motor symptoms and vice versa, which is important to take into account in the treatment of both anxiety and motor symptoms in PD patients.

Besides PD, other progressive neurological disorders such as MS and Huntington's disease are also accompanied by both motor and psychiatric symptoms [15, 16]. Resulting from our meta-analyses in **chapter 6**, psychological treatments show small to moderate effects in reducing psychiatric symptoms in patients with PD and MS, which indicates that treatments can be optimized. Optimizing psychological treatments could include taking the interactions with motor symptoms into account. Since the nature of neurodegenerative diseases involves progressive decline and inevitability of occurring symptoms, especially motor symptoms, the effects on symptom reduction can be expected to be unsatisfactory. The effect on psychiatric symptoms, however, can result in reduction of psychiatric symptoms. The interaction with inevitable motor symptoms, thereafter, makes the treatment of psychiatric symptoms in PD patients challenging.

Especially regarding wearing-off, it is important to discuss treatment options to improve motor symptom fluctuations. First line treatment in improving motor as well as non-motor fluctuations is dopamine replacement therapy [17]. When motor symptom fluctuations diminish, non-motor symptoms (including anxiety) might also diminish [18]. However, available pharmacological treatments are considered insufficient to alleviate the complications (e.g. response fluctuations) of PD [19]. Also, a small percentage of patients can develop a dopamine dysregulation syndrome

(DDS) as a complication of dopamine replacement therapy, especially when the accompanied anxiety remains untreated [20, 21]. DDS is an impulse control disorder characterized by an addiction-like PD medication overuse [22].

One can also consider more advanced treatment options, such as Deep Brain Stimulation (DBS), continuous levodopa-carbidopa intestinal gel infusion, and continuous subcutaneous apomorphine infusion. These advanced treatment options are considered when PD patients experience debilitating response fluctuations and/or dyskinesias in spite of optimal dopamine replacement therapy [23]. However, since PD is a neurodegenerative disease in which progressive decline is inevitable, patients eventually still develop symptom fluctuations and the abovementioned advanced therapies are considered rather invasive and/or contraindicated in some patients.

It is therefore warranted to explore non-pharmacological and non-invasive treatments, to teach PD patients longterm coping strategies in order to deal with symptom fluctuations and interactions, as is also suggested by some of the studies included in our meta-analyses in **chapter 6** [24-26]. To achieve acceptance of symptoms and healthy coping strategies, it is important to increase awareness of ones bodily symptoms, thoughts and emotions [27]. Especially, it is important to improve interoceptive accuracy, which refers to the accurate sensing of internal bodily changes, which includes both awareness and interpretation of bodily sensations [27]. Based on our clinical experience with PD patients that experience wearing-off related anxiety, we see inaccuracies in body awareness, which is an element of interoception. These inaccuracies can present themselves as either a hyperawareness or an unawareness. Hyperawareness refers to an excessive focus on bodily sensations and is characteristic in patients with an anxiety disorder, especially panic disorder [28-30]. A common factor in anxiety disorders is an attentional bias toward threat [28], and when one interprets bodily sensations as dangerous, hyperawareness on these sensations is a logical consequence and is evidenced to increase anxiety [30-32].

Unawareness can be seen as avoidance behavior, which can result in an overwhelming sense of anxiety (e.g. panic attack) when bodily sensations are so intense they cannot longer be ignored. Patients with functional neurological symptoms, chronic pain, and somatoform disorders show lower interoceptive accuracy [33-35]. In addition, reduced interoceptive accuracy was predictive of depressive symptoms [34] and correlated with symptom severity in these patients [33].

Body awareness and interoceptive accuracy have not yet been investigated in patients with PD. Based on the overlap with somatic symptom and related disorders and anxiety disorders, we hypothesize that it would be helpful to improve interoceptive accuracy and subsequently alter the catastrophic interpretations of bodily sensations, in order to bring body awareness to a more healthy and neutral experience. This is specifically relevant for PD patients that experience wearing-off related anxiety, where motor symptoms directly interact with anxiety symptoms.

Body awareness therapies show positive results in patients with chronic pain and somatic symptom and related disorders [36, 37]. In the treatment of patients with chronic pain, positive effects are also found regarding multidisciplinary treatment in which body awareness therapy is included [36]. The *BEWARE* training (**chapters 7 and 8**) was the first attempt in improving body awareness and in addressing the complex interactions between motor and anxiety symptoms in PD, by combining physical therapy with Acceptance and Commitment Therapy (ACT). Besides body awareness and learning how to cope with the complex symptom interactions, the *BEWARE* training also focuses on acceptance and incorporates exposure as an important element in the treatment of anxiety.

Patients with intact cognitive abilities benefited the most from the *BEWARE* training, which indicates that the treatment requires cognitive abilities to be largely intact. Reflecting upon the non-significant results on the primary outcome measure self-efficacy, the items on this questionnaire mainly concern problem solving. However, the progressive debilitating symptoms of PD cannot always be solved. At the time of designing the pilot-RCT, there was no suitable outcome measure available in Dutch to really grasp the intention or goal of ACT, namely the acceptance and commitment to valued living despite of the debilitating symptoms. We are currently investigating an imnproved version of the *BEWARE* treatment in a multicenter RCT. Now, we use the Chronic Illness Acceptance Questionnaire (CIAQ) as a primary outcome measure, which may be more suitable for the goal of the treatment. Since the CIAQ was not available in Dutch and is not validated in PD patients, we officially translated (and back-translated) the CIAQ and are investigating its validity and reliability in an independent group of PD patients.

In clinical research, and specifically in investigating the effectiveness of a treatment, it is important to take the patients' experience and perspective into consideration. Patients can give valuable information about what they find most troublesome in dealing with their disease, what helps them the most or what is effective in treating their symptoms, and what is considered to have the highest impact on

their lives. Practical suggestions for improvement in the *BEWARE* study, both for the treatment and study design, resulted from qualitative assessments in which patient researchers from the Dutch Parkinson Patient Association (Parkinson Vereniging) performed interviews with the participating patients. We incorporated these suggestions to improve the *BEWARE* treatment and our study design.

To date, the *BEWARE* study is the only RCT that investigated a treatment for anxiety in PD patients and is anxiety still considered to be an ignored but important aspect of PD [19]. Because of the co-occurrence of motor and mental symptoms, we recommend treating anxiety in PD in a multidisciplinary manner, increasing effectiveness using a holistic approach. In this way, we can break through the vicious cycle of subsequent motor and anxiety symptoms. For PD patients that experience wearing-off related anxiety, one can imagine this makes the wearing-off experience less stressful and increases psychological wellbeing [6].

Methodological considerations

The methodological strengths and limitations were discussed in each individual chapter. Here we summarize and further discuss important strengths and limitations of the research in this thesis.

A major strength of this thesis is the use of different statistical techniques that together provide important insights in the complex relationships between motor and non-motor symptoms, mainly anxiety, in PD. The different symptom dimensions of anxiety were first investigated in a large patient sample (**chapter 2**) and were replicated in a patient sample with considerable neuropsychiatric symptoms (**chapter 3**), which improves the generalizability of our findings. Cross-sectional associations were investigated in large patient samples (**chapters 2, 3, and 4**) using principal component analyses and network analysis, from which we gained insights in these associations on the level of anxiety dimensions and on single symptom-level. The principal component analyses address the shared variation amongst symptoms, while the network analysis shows unique symptom-to-symptom variations within different patient groups [38]. The longitudinal study design in **chapter 5** allowed us to draw conclusions regarding temporal relationships and the influence of possible confounders between motor and anxiety symptoms in PD. Another major strength of this thesis is that we investigated the first multidisciplinary treatment combining ACT and physical therapy using an RCT design (**chapters 7 and 8**). Moreover, it is the first and only RCT investigating a treatment for anxiety in PD to date. In this RCT, we collaborated closely with patient researchers of the Dutch Parkinson Patient

Association (Parkinson Vereniging) which enabled us to systematically involve the patients to further improve the *BEWARE* training.

Nonetheless, there are some methodological limitations that are important to discuss. First of all, the BAI was used in three of our studies, in which we investigated the cross-sectional associations (**chapters 2 through 4**). The BAI is considered not the most reliable measure of anxiety in PD patients, since it contains mainly items measuring episodic forms of anxiety, disregarding non-episodic forms of anxiety such as generalized anxiety disorder, which is the most common anxiety disorder in PD [39, 40]. For future research, it is therefore recommended to use, for example, the Parkinson Anxiety Scale (PAS) developed by Leentjens and colleagues [41], which includes items referring to both episodic and non-episodic forms of anxiety. Also, it includes avoidance behaviours, which is an important part of anxiety [8].

In **chapter 5** we used the Hospital Anxiety and Depression Scale to assess anxiety symptoms on multiple time points to investigate longitudinal relationships. Measurements were three weeks apart, which did not allow us to investigate the motor – anxiety interactions over shorter periods of time (e.g. minutes or hours), which might be more interesting in PD patients with fluctuations. In addition, the questionnaires that were used inquired about symptoms over different time periods, e.g. one versus four weeks, which resulted in average scores over different time periods and refrained us from drawing causal conclusions about symptom interactions. The associations investigated in **chapters 2 through 5** showed that motor and anxiety symptoms can co-occur, however, the interactions might be better investigated using time-series data in which symptom measurements are performed in much shorter time intervals (e.g. multiple times a day) using, for example, expierence sampling method.

Regarding anxiety diagnoses, the diagnosis that patients received in **chapter 3** was not assessed through a structural clinical interview, but through psychiatric evaluation in daily clinical practice. Although the primary diagnosis was correctly reported, secondary diagnoses of anxiety might not always have been reported, mainly in cases with a primary psychiatric disorder that could also explain the present anxiety symptoms (e.g. psychotic disorder, parkinson's disease dementia). A structured interview might have resulted in more secondary anxiety diagnoses.

Unfortunately, in the PD patient sample used in **chapter 4**, data on psychiatric diagnoses were not available to divide our patient group on whether or not patients had an anxiety disorder. We divided the patient group into high- versus low-anxious

patients on based on the total score on the BAI (cut-off >12) [42]. This might have resulted in some false positive associations between BAI-items in the network. Although the patient groups were relatively large (316 and 253 PD patients) and we corrected for multiple comparisons, for this type of analysis it is preferred to test even larger groups [43]. It is therefore important to interpret the results of this chapter with caution.

The described *BEWARE* training in **chapters 7 and 8** and the studies included in the meta-analyses described in **chapter 6** included small numbers of participants. This results in low power, and therefore we cannot draw hard conclusions concerning the effectiveness of psychological treatments. Although the psychological treatments and the *BEWARE* training show promising results, there is room for improvement.

Suggestions for future research

This thesis elaborately investigated the complex interactions between motor and non-motor symptoms in PD patients, including the treatment of anxiety in the context of response fluctuations. However, more research is needed to fully understand these complex interactions to improve diagnosis of anxiety and wearing-off related distress and its treatment.

Since these complex interactions are very much apparent in PD patients with fluctuations, we expect that in these patients the interactions might be even more evident when symptoms are measured in shorter time periods (e.g. minutes or hours). For example, a panic attack occurs suddenly [8] and usually diminishes within several minutes. PD patients that experience panic attacks in the context of wearing-off related anxiety can experience subsequent symptoms that occur in a time-period of minutes. To further investigate symptom interactions, it is therefore recommended to apply methods with more finegrained time resolution to study interactions between motor, automic and affective symptoms of response fluctuations. An interesting example of such approach is the N = 1 study performed by van der Velden and colleagues [44], investigating time-series data from an individual patient using network analysis. Building onto our own research, it would be interesting to include both somatic symptoms (such as freezing, tremor, rigidity, and autonomic symptoms) as well as cognitive of affective anxiety symptoms (such as fear of losing control and rumination). We hypothesize that, in anticipation of an 'off' period, patients feel more tense and therefore experience an earlier onset of or a more severe subsequent 'off' period. In addition, by using time-series data in a network analysis for a single PD patient, we can investigate which symptoms interact with other symptoms and are therefore potential treatment targets. This might

be very useful in clinical practice, and facilitates a more personalized treatment approach.

Research on the treatment of anxiety in PD, and especially in the context of motor symptoms, is extremely limited. More research is warranted, both pharmacological and non-pharmacological, in order to treat anxiety in PD more effectively. We investigated a multidisciplinary treatment combining Acceptance & Commitment therapy with physical therapy. This showed promising results and together with the feedback of the participants, we optimized this *BEWARE* training, and we are currently investigating its effectivity in a better powered multicenter study. When the *BEWARE* training is considered effective, we intend to optimize the treatment further and add an online training module in order for patients to practice more intensively at home. Since patients with intact cognitive abilities benefited the most from *BEWARE,* it would be interesting to develop a more behavioural variant of the treatment that demands less cognitive abilities. In this variant, the primary focus lies on behavioural change. The Patient Education Program Parkinson (PEPP) also incorporated a more behavioural option in their CBT-based program, showing good results [45]. After proving its effectiveness, the *BEWARE* treatment can be implemented in clinical practice. Implementation is achieved by training therapists in the treatment protocol and making the treatment available for patients through health care providers. Ideally, in order to increase evidence for its effectiveness, the treatment needs to be investigated in an independent PD patient sample.

Final conclusions

PD is characterized by a variety of motor and non-motor symptoms. This thesis confirms that consideration of motor and other PD-related symptoms is important in diagnosing anxiety and in the treatment of response fluctuations. The reciprocal associations between motor and anxiety symptoms should be taken into account in both the diagnostic and treatment process. Especially the temporal interactions of these symptoms are in need of further investigation, as well as alternative treatment options for anxiety and wearing-off in PD.

The suggested strong interplay between motor and non-motor symptoms in PD warrants a holistic approach to treatment of anxiety in clinical practice. The *BEWARE* training is the first attempt to treat anxiety in a multidisciplinary manner, in the context of response fluctuations with the aim to improve coping and valued living in spite of (inevitable) PD symptoms.

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A

English summary

Parkinson's disease (PD) is a neurodegenerative disorder with a prevalence of 100 to 200 per 100,000 people and an annual incidence of 15 per 100,000 people. Due to ageing and other factors such as genetic mutations and environmental risk factors (e.g. pesticides), the occurrence of PD is increasing. Recently, PD has even been described as a pandemic.

PD is characterized by its main motor symptoms bradykinesia, rigidity and tremor, and additional motor and non-motor symptoms. Non-motor characteristics may include cognitive dysfunction, autonomic failure, and neuropsychiatric symptoms and disorders such as anxiety, depression, psychosis, impulse control disorders, sleep disorders, and apathy.

As compared to the motor symptoms, neuropsychiatric symptoms are often reported to have a higher impact on quality of life of both patients and their caregivers. Amongst neuropsychiatric symptoms, anxiety and depression are considered major predictors of reduced quality of life, followed by cognitive dysfunction.

Currently, up to 45% of PD patients experience either clinically relevant anxiety symptoms or fulfill the criteria for an anxiety disorder, including generalized anxiety disorder, panic attacks, and social phobia. Anxiety in PD can also occur in the context of response fluctuations in PD symptoms, especially related to wearing-off, i.e., the re-emergence of PD symptoms while transitioning from an 'on' state to an 'off' state, typically occurring prior to the next scheduled dose of dopaminergic medication taking effect. About 75% of patients with motor fluctuations experience fluctuations in mood and/or anxiety in parallel. Therefore, diagnosing and treating anxiety in PD is complicated, due to overlapping motor and autonomic symptoms, comorbid psychiatric symptoms, and the interplay between anxiety and motor symptoms over time.

This thesis mainly focuses on understanding (part 1) and treating (part 2) anxiety symptoms in the context of motor symptoms. **Chapter 1** provides a general introduction on anxiety in PD including the multiple factors that complicate diagnosis and treatment.

The first part of this thesis (**chapters 2 through 5**) focuses on understanding the complex associations and interactions between anxiety, motor and other non-motor

symptoms in PD. In **chapter 2** we investigated the phenomenology of anxiety in PD by performing a principal component analysis on the items of the Beck Anxiety Inventory (BAI) in a sample of 294 PD patients to explore underlying symptom dimensions and to relate these to other motor and non-motor features. We showed that the BAI consists of one *affective* (clustering anxious cognitions and emotions) and four *somatic* symptom subscales (clustering physical symptoms). We found significant associations between the somatic subscales and motor and autonomic symptoms, as measured with the UPDRS-III and SCOPA-AUT, respectively. The affective subscale showed a significant association with depressive symptoms (as measured with the BDI), but no association with motor or autonomic symptoms.

To investigate the generalizability of the findings in chapter 2, **chapter 3** describes the replication of the principal component analysis in 123 PD patients that were referred for neuropsychiatric evaluation to a specialized neuropsychiatric outpatient department. Again, we found one affective and four somatic anxiety symptom subscales, and a strong association between anxiety and depression. In a post-hoc analysis, the score on the affective subscale showed equal predictive value as compared to the total BAI score in predicting whether or not patients received an anxiety disorder diagnosis through psychiatric evaluation. The associations of the subscales of the BAI with the BDI, UPDRS-III and SCOPA-AUT confirm the overlap of anxiety in PD with both depression and with motor and autonomic symptoms. The *affective* subscale might be used to screen for anxiety in order to eliminate somatic equivalents of anxiety that can also be interpreted as motor or autonomic PD symptoms. However, we do not recommend to disregard the somatic symptoms completely, and rather suggest to interpret anxiety symptoms in the context of motor symptoms, taking this overlap and interaction into consideration.

To investigate whether the associations between motor symptoms and anxiety differed in strength between high- versus low-anxiety PD patients, we used an explorative network analysis to study these associations in **chapter 4**. In the high-anxiety group, 316 PD patients were included, in the low-anxiety group, 253 PD patients were included. The high-anxiety PD patient network showed higher global strength. In spite of group differences in clinical and demographic characteristics, with the high-anxious group showing significantly worse motor and cognitive function, a higher age, and more female patients, the network comparison test did not show statistically significant differences in strength of the connections between motor and anxiety symptoms. Since associations between motor and anxiety symptoms are apparent in both groups, this shows that these symptoms are associated, even when patients have no to mild anxiety symptoms.

Chapters 2,3, and 4 focused on the associations between motor, anxiety, and other symptoms, not taking into account their temporal relationships. As symptom intensity may vary over time, we investigated the longitudinal associations between anxiety, fear of falling, and freezing of gait in 153 PD patients in **chapter 5**. Across four measurements, with three weeks between each measurement, all associations were significant, with the strongest association between fear of falling and freezing of gait. Adjustments for disease characteristics (such as disease duration, depressive and cognitive symptoms) and adverse effects of medication (such as response fluctuations) diminished all associations, which confirms the complex interactions between motor and anxiety symptoms.

After a description of the phenomenology of anxiety, and its cross-sectional and longitudinal associations with motor and other non-motor symptoms, part 2 of this PhD thesis focuses on the treatment of these complex symptom interactions in PD patients.

In **chapter 6**, we describe two meta-analyses on the effects of cognitive behavioral therapy and mindfulness-based therapies on psychological distress in patients with neurodegenerative disorders. The included studies were divided into those comparing the treatment of interest with an active control condition and those with a treatment as usual or waitlist control condition. The results showed that psychological interventions have a small to moderate effect on reducing psychological distress in patients with PD and Multiple Sclerosis (MS). The overall quality of the included studies was low and showed considerable heterogeneity, which pleads for more studies with better quality.

Chapters 7 and 8 present the study protocol and results of a pilot randomized controlled trial (RCT) in which we described and investigated a newly developed multidisciplinary group treatment for wearing-off related anxiety in PD named *BEWARE*. *BEWARE* is a body awareness group training in which we combine elements from acceptance and commitment therapy (ACT) with physical therapy. We compared the *BEWARE* training with group physical therapy. In **chapter 8** we describe the results of this pilot RCT. Patients that participated in the *BEWARE* training showed no significant improvement in the primary outcome measure, self-efficacy, as compared to the control condition. However, this group did show a more improved emotional wellbeing as well as standing balance, both at post-treatment and follow-up. Feelings of social stigmatization decreased as well, however, the difference with the control group was not statistically significant. The *BEWARE* training was the first attempt in improving body awareness and in addressing the

complex interactions between motor and anxiety symptoms in PD. An optimized Beware intervention is currently being investigated in a large multicenter RCT.

Finally, in **Chapter 9**, the findings of this thesis are summarized and reflected upon. I describe the reciprocal interactions between anxiety, motor, and autonomic symptoms. I link our findings to the research field on body awareness in psychosomatic disorders, discussing the commonalities in the inaccuracy of interpretation of bodily symptoms that is seen in both PD patients with wearing-off related anxiety and patients with psychosomatic disorders. Subsequently, I provide suggestions for improving this inaccuracy. Regarding the reciprocal interactions between motor and anxiety symptoms, I discuss how this interaction should be taken into account through multidisciplinary treatment, of which the BEWARE training is a first attempt in PD. This thesis helps to understand and treat anxiety symptoms in the context of motor symptoms in PD patients, aiming to improve psychological wellbeing irrespective of disease progression. Since patients experience symptom fluctuations during the day, I provide suggestions for more in-depth investigation of interactions between motor and anxiety symptoms during response fluctuations, for which we propose using high-frequent time-series data.

Nederlandse samenvatting

De ziekte van Parkinson (ZvP) is een neurodegeneratieve aandoening met een prevalentie van 100 tot 200 per 100.000 mensen, en een jaarlijkse incidentie van 15 per 100.000 mensen. Door veroudering en andere factoren zoals genetische mutaties en omgevingsrisicofactoren (bijv. Pesticiden), neemt het voorkomen van de ZvP toe. Onlangs werd de ziekte zelfs omschreven als een pandemie.

De ZvP wordt gekenmerkt door de belangrijkste motorische symptomen bradykinesie, stijfheid en tremor, en bijkomende motorische en niet-motorische symptomen. Niet-motorische symptomen kunnen cognitieve disfunctie, autonoom falen en neuropsychiatrische symptomen en stoornissen zijn, zoals angst, depressie, psychose, stoornissen in de impulsbeheersing, slaapstoornissen en apathie.

In vergelijking met de motorische symptomen, wordt vaak gemeld dat neuropsychiatrische symptomen een grotere invloed hebben op de kwaliteit van leven van zowel patiënten als hun naasten. Van de neuropsychiatrische symptomen worden angst en depressie beschouwd als belangrijkste voorspellers van verminderde kwaliteit van leven, gevolgd door cognitieve disfunctie.

Momenteel ervaart tot 45% van de Parkinson-patiënten klinisch relevante angstsymptomen of voldoet aan de criteria voor een angststoornis, waaronder gegeneraliseerde angststoornis, paniekaanvallen en sociale fobie. Angst bij de ZvP kan ook optreden in de context van responsfluctuaties, vooral gerelateerd aan het opnieuw optreden van Parkinson-symptomen tijdens de overgang van een 'on'-toestand naar een 'off'-toestand, die meestal optreedt vlak vóór de volgende geplande dosis dopaminerge medicatie. Ongeveer 75% van de patiënten met motorische fluctuaties ervaart tegelijkertijd stemmingswisselingen en/of angst. Het diagnosticeren en behandelen van angst bij Parkinson is gecompliceerd vanwege overlappende motorische en autonome symptomen, comorbide psychiatrische symptomen (zoals depressie) en de wisselwerking tussen angst- en motorische symptomen in de loop van de tijd.

Dit proefschrift richt zich voornamelijk op het begrijpen (deel 1) en behandelen (deel 2) van angstsymptomen in de context van motorische symptomen. **Hoofdstuk**

1 geeft een algemene inleiding over angst bij de ZvP, inclusief de vele factoren die diagnosticeren en behandelen bemoeilijken.

Het eerste deel van dit proefschrift (**hoofdstukken 2 t/m 5**) richt zich op het begrijpen van de complexe associaties en interacties tussen angst, motorische en andere niet-motorische symptomen bij de ZvP. In **hoofdstuk 2** onderzochten we de fenomenologie van angst bij de ZvP door een principale componentenanalyse uit te voeren op de items van de Beck Anxiety Inventory (BAI), in een steekproef van 294 Parkinson-patiënten, om onderliggende symptoomdimensies te onderzoeken en deze te relateren aan andere motorische en niet- motorische symptomen. We toonden aan dat de BAI bestaat uit één *affectieve* (clustering van angstige cognities en emoties) en vier *somatische* symptoomsubschalen (clustering van fysieke symptomen). We vonden significante associaties tussen de somatische subschalen en motorische en autonome symptomen, zoals gemeten met de UPDRS-III en SCOPA-AUT, respectievelijk. De affectieve subschaal vertoonde een significant verband met depressieve symptomen (zoals gemeten met de BDI), en had geen verband met motorische of autonome symptomen.

Om de generaliseerbaarheid van de bevindingen in hoofdstuk 2 te onderzoeken, beschrijft **hoofdstuk 3** de replicatie van de principale componentenanalyse bij 123 Parkinson-patiënten die voor neuropsychiatrische evaluatie waren verwezen naar een gespecialiseerde neuropsychiatrische polikliniek. Opnieuw vonden we een *affectieve* en vier *somatische* subschalen, en een sterke associatie tussen angst en depressie. In een post-hoc analyse vertoonde de score op de *affectieve* subschaal dezelfde voorspellende waarde als de totale BAI-score bij het voorspellen of patiënten al dan niet een diagnose van een angststoornis kregen door middel van psychiatrische evaluatie. De associaties van de subschalen van de BAI met de BDI, UPDRS-III en SCOPA-AUT bevestigen de overlap van angst bij Parkinson met zowel depressieve als met motorische en autonome symptomen. De *affectieve* subschaal kan worden gebruikt om op angst te screenen om somatische equivalenten van angst te elimineren die ook kunnen worden geïnterpreteerd als motorische of autonome Parkinson-symptomen. Echter, raden we niet aan om de somatische symptomen volledig te negeren, en angstsymptomen in het kader van de motorische symptomen te interpreteren, deze overlap en interactie in overweging nemende.

Om te onderzoeken of de associaties tussen motorische symptomen en angst verschilden in sterkte tussen Parkinson-patiënten met hoge en lage angst, hebben we een exploratieve netwerkanalyse gebruikt om deze associaties te

bestuderen in **hoofdstuk 4**. In de groep met hoge angst werden 316 Parkinson-patiënten geïncludeerd, in de groep met lage angst 253 Parkinson-patiënten. Het angstige patiëntennetwerk vertoonde een grotere algehele sterkte. Ondanks de groepsverschillen op klinische en demografische kenmerken, waarbij de angstige patiëntengroep aanzienlijk slechter motorisch en cognitieve functioneren liet zien, een hogere leeftijd en meer vrouwelijke patiënten bevatte, leverde de netwerk-vergelijkingstest geen statistisch significante verschillen op in de sterkte van de verbanden tussen motorische en angstsymptomen. Aangezien associaties tussen motorische en angstsymptomen in beide groepen aanwezig zijn, toont dit aan dat deze symptomen geassocieerd zijn onafhankelijk van hun angstniveau.

De hoofdstukken 2, 3 en 4 waren gericht op de associaties tussen motoriek, angst, en andere symptomen, zonder rekening te houden met hun relaties over de tijd. In **hoofdstuk 5** onderzochten we de longitudinale verbanden tussen angst, angst om te vallen, en freezing (bevriezing van het lopen) bij 153 patiënten met de ZvP. Over vier metingen, met drie weken tussen elke meting, waren alle associaties significant, met de sterkste associatie tussen angst om te vallen en freezing. Aanpassingen voor ziektekenmerken (zoals ziekteduur, depressieve en cognitieve klachten) en bijwerkingen van medicatie (zoals responsfluctuaties) verminderden alle associaties, wat de complexe interacties tussen motorische en angstsymptomen bevestigt.

Na een beschrijving van de fenomenologie van angst, en de cross-sectionele en longitudinale associaties met motorische en andere niet-motorische symptomen, richt deel 2 van dit proefschrift zich op de behandeling van deze complexe symptoominteracties bij Parkinson-patiënten.

In **hoofdstuk 6** beschrijven we twee meta-analyses naar de effecten van cognitieve gedragstherapie en op mindfulness gebaseerde therapieën op psychische problemen bij patiënten met neurodegeneratieve aandoeningen. De geïncludeerde onderzoeken werden verdeeld in een groep met een actieve controle conditie en een groep met een gebruikelijke behandeling of wachtlijst controle conditie. De resultaten toonden aan dat psychologische interventies een klein tot matig effect hebben op het verminderen van psychisch leed bij patiënten met de ZvP en Multiple Sclerose (MS). De algehele kwaliteit van de geïncludeerde onderzoeken was laag en vertoonde een aanzienlijke heterogeniteit, wat pleit voor meer onderzoeken met betere kwaliteit.

Hoofdstukken 7 en 8 presenteren het studieprotocol en de resultaten van een pilot gerandomiseerde gecontroleerde trial (RCT) waarin we een nieuw ontwikkelde multidisciplinaire groepsbehandeling voor angst in het kader van responsfluctuaties bij patiënten met de ZvP, genaamd *BEWARE*, hebben beschreven en onderzocht. *BEWARE* is een groepstraining voor lichaamsbewustzijn waarin we elementen van acceptance and commitment therapie (ACT) combineren met fysiotherapie. We vergeleken de *BEWARE*-training met fysiotherapie in groepsverband. In **hoofdstuk 8** beschrijven we de resultaten van deze pilot RCT. Patiënten die deelnamen aan de *BEWARE*-training toonde geen significante verbetering in de primaire uitkomstmaat, zelfredzaamheid, in vergelijking met de controle conditie. Echter, deze groep liet wel een verbetering in emotioneel welzijn en staande balans zien, zowel direct na de behandeling als 3 maanden na de behandeling. Gevoelens van sociale stigmatisering namen ook af, maar het verschil met de controlegroep was niet statistisch significant. De *BEWARE*-training was de eerste poging om het lichaamsbewustzijn te verbeteren en de complexe interacties tussen motorische en angstsymptomen bij de ZvP geïntegreerd te behandelen. Een geoptimaliseerde BEWARE-interventie wordt momenteel onderzocht in een grote multicenter RCT.

Tenslotte, in **hoofdstuk 9**, worden de resultaten van dit onderzoek samengevat en overdacht. Ik beschrijf de wederzijdse interacties tussen angst, motorische en autonome symptomen. Ik link onze bevindingen aan het onderzoek over lichaamsbewustzijn bij patiënten met een psychosomatische stoornis, en ik bespreek de overeenkomsten in de misinterpretatie van lichamelijke signalen die wordt gezien in zowel Parkinson-patiënten met angst gerelateerd aan responsfluctuaties, als in patiënten met een psychosomatische stoornis. Vervolgens doe ik suggesties om deze misinterpretatie te verbeteren. Wat betreft de wederzijdse interacties tussen motorische en angstsymptomen, bespreek ik hoe we met deze interacties rekening moeten houden door middel van multidisciplinaire behandeling, waarvan de *BEWARE*-training een eerste poging is bij de ZvP. Dit proefschrift helpt bij het begrijpen en behandelen van angstsymptomen in de context van motorische symptomen bij Parkinson-patiënten, met als doel het psychologisch welzijn te verbeteren, ongeacht de progressie van de ziekte. Aangezien symptomen bij Parkinson-patiënten kunnen schommelen gedurende de dag, bied ik suggesties om meer diepgaand onderzoek te doen naar de interacties tussen motorische en angstsymptomen tijdens responsfluctuaties, waarbij gebruik kan worden gemaakt van meerdere meetmomenten per patiënt per dag.

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I.P.H. (Ires) Ghielen (2021). Surfing the waves of Parkinson's disease. Understanding and treating anxiety in the context of motor symptoms. Vrije Universiteit Amsterdam. ISBN: 978-94-6416-493-0

Portfolio

Courses		Year	ECTS
BROK course, Amsterdam		2014 & 2018	1.5
Scientific Integrity course, Amsterdam		2017	2
Statistics course “Multilevel analysis” (EpidM), Amsterdam		2017	2
Grant writing course (Utrecht University & Elevate Health)		2017	3
PPEP4all course (Boerhave nascholing), Leiden		2017	2
ACT course (SeeTrue), Amsterdam		2018	4
Conferences			
ACBS conference New Orleans (Online)	poster	2020	2
ParkinsonNet Rotterdam	workshop	2017	0.5
ParkinsonNet Nieuwegein	workshop + poster	2019	0.5
Voorjaarscongres Psychiatrie Maastricht	oral	2018	0.2
Najaarscongres VGCt	oral	2018	0.2
Other			
Brein in Beeld; educative workshops for kids		2017-2018	2
Supervising interns		2017-2020	5
Presentation for lay audiences		2017-2020	1
Participation internal meetings & seminars		2017-2020	5
Awards & grants			
2nd poster prize Science Exchange Day		2017	
Grant from the Netherlands Brain Foundation (Hersenstichting - Sneller Beter Behandelen) – €300.000		2017	

Dankwoord

Voor mijn dankwoord moet ik eigenlijk terug naar 8 jaar geleden, toen mijn tijd bij de afdelingen psychiatrie en Anatomie & Neurowetenschappen, sectie Neuropsychiatrie begon. Want vanaf toen is de weg ingezet waardoor mijn promotie, en nog zoveel andere dingen, op mijn pad zijn gekomen.

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Anders; so far away but sometimes very close, what I absolutely enjoy so much! Hopefully you will be visiting us soon and can I visit you again in Norway. Maybe a hike together? :-) Thank you for all your kindness, hospitality, and love.

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About the author

Ires Ghielen was born on October 29, 1990 in Helden. She grew up with a younger brother and both her parents in the village of Beringe. At the end of her athenaeum studies at high schools Bouwens van der Boijecollege in Panningen and the VAVO in Venlo, her grandfather got diagnosed with Parkinson's disease (PD). When she gained some knowledge about the disease, and saw how the disease impacts the lives of her grandfather and her family as a whole, she decided to become a researcher and help PD patients. Therefore, in 2010, she moved to Amsterdam to study Psychobiology at the University of Amsterdam. After a research-internship in which she came into contact with a lot of PD patients, Ires' ambition for combining research with clinical work grew. After obtaining her Bachelor's degree, she transferred to a Research Master in Clinical Neuropsychology and she took a clinical internship at the Medical Psychology department of Amsterdam UMC, location VUmc. She obtained her Master's degree in 2017.

Ires' first employment was in 2014 at the University of Amsterdam, where she was a teaching assistant in statistics for first-year students. Within the same year, she started working as a research assistant at the department of Anatomy and Neuroscience within the Amsterdam UMC, location VUmc. For more than one year, she coordinated the Randomized Controlled Trial (RCT) named BEWARE under the guidance of prof. dr. Odile A. van den Heuvel and dr. Erwin E.H. van Wegen, which became an important part of this thesis. The BEWARE project investigates a multidisciplinary group treatment combining physical therapy with psychotherapy in order to learn PD patients to better cope with their fluctuating motor and anxiety symptoms. In 2017, Ires got the opportunity to start a PhD position on this very same project and set up an improved and more extensive RCT, collaborating with two other centers to further investigate the BEWARE treatment. This project was supervised by promotor prof. dr. Odile A. van den Heuvel, promotor dr. Erwin E.H. van Wegen, and copromotor dr. Sonja Rutten. Together with her promoters, Ires received a grant from the Hersenstichting to financially support this research project.

Besides her PhD position, Ires also started a post-master education for health care (GZ-)psychologist at RINO Amsterdam and GGZ ingeest in 2017. She specifically gained practical experience in diagnosing and treating patients with psychosomatic and anxiety disorders.

In 2020, Ires started her online business: Hulp bij Wetenschappelijk Onderzoek. She helps health care professionals in doing their scientific research. After finishing her PhD, Ires will continue her work as a researcher within her online business. Still within her ambition to combine research with clinical practice, she will also continue her work with patients as a health care (GZ-)psychologist within the field of Neuropsychology. Ires currently lives in Wormerveer with her partner Jean Paul.